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Acute Rheumatic Fever in the Young Adult White Male. By JAMES G. HIRSCH, M.D., and DAVID M. FLETT, M.D. 599

The Incidence and Cost of Treatment of Bacterial Endocarditis. By HARRY F. DOWLING, M.D., and FRANCIS J. MURRAY, M.D. 612

A Study of the Antigen-Antibody Mechanism in Rheumatic Diseases. By THOMAS McP. BROWN, M.D., RUTH H. WICHELHAUSEN, M.D., WILLIAM R. MERCHANT, M.D., and LUCILLE B. ROBINSON, A.B. 618

Plasma Protein-Bound Iodine Determinations. By WILLIAM N. HARSHA, M.D. 626

Sickle Cell Disease: Studies on "In Vivo" Sickling and the Effect of Certain Pharmacological Agents. By A. B. HENDERSON, M.D. 628

An Appraisal of Transorbital Leukotomy. By MATTHEW T. MOORE, M.D. 636

The Musical Murmur of Aortic Insufficiency. By DAVID GELFAND, M.D., and SAMUEL BELLET, M.D. 644

The Treatment of Urgent Cases of Paroxysmal Auricular Fibrillation. By EMANUEL HELLMAN, M.D., M. RICHARD ALTCHECK, M.D., and CHARLES D. ENSELBERG, M.D. 655

The Vasodilator Effects of Priscoline in Patients with Ischemic Extremities. By HANS ROTTENSTEIN, M.D., ORVILLE HORWITZ, M.D., HUGH MONTGOMERY, M.D., ANN SAYEN, and LAWRENCE L. SIEMS, M.D. 661

Digital Cutaneous Blood Flow, Cardiac Output, Blood Pressure and Pulse Rate Immediately Following the Administration of Four Potential Vasodilators. By ANN SAYEN, ORVILLE HORWITZ, M.D., and MORRIS W. STROUD, 3RD, M.D. 667

Measurements of Certain Cardiovascular Responses to ACTH and Cortisone in Man. By ORVILLE HORWITZ, M.D., ANN SAYEN, MEYER NAIDE, M.D., and JOSEPH LEE HOLLANDER, M.D. 669

The Production of Urinary Casts During the Use of Cation Exchange Resins. By I. S. FRIEDMAN, M.D., S. ZUCKERMAN, M.D., and T. D. COHN, M.D. 672

Observations on the Plasma Potassium Level of Man. By S. J. FARBER, M.D., E. D. PELLEGRINO, M.D., N. J. CONAN, M.D., and D. P. EARLE, M.D. 678

The Effect of Aureomycin on Venous Clotting Time. By WILLIAM A. BLODGETT, M.D., and FRED J. SCHILLING, M.D. 688

Progress of Medical Science

Gynecology and Obstetrics. CARL BACHMAN, M.D., and FRANK B. BLOCK, M.D. 691

Pediatrics. IRVING J. WOLMAN, M.D. 699

Proceedings of the Physiological Society of Philadelphia 712

Complete contents on adv. page 10

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JUNE, 1951

ORIGINAL ARTICLES

ACUTE RHEUMATIC FEVER IN THE YOUNG ADULT WHITE MALE

By James G. Hirsch*, M.D.

AND

David M. Flett, M.D.

(From the Medical Service, Station Hospital, Francis E. Warren Air Force Base, Cheyenne, Wyoming)

It is well recognized that the natural history of acute rheumatic fever varies according to the age, sex, and race of the individual afflicted with this disease. Although the clinical features of rheumatism in general have been well documented in the voluminous literature dealing with this topic, our knowledge of the characteristics of this illness in certain groups of patients remains incomplete. Relatively speaking, little information is available concerning the natural history of active rheumatic fever in young adult white males. Most of the reports containing information pertaining to this subject were made following observations in armed forces installations during World War II[6,7,10,13,27-29,37,38,43,44]. In many instances these studies were of necessity somewhat lacking in completeness or in continuity as a result of the exigency of the times.

During a 2-year period in 1948–1949, 109 cases of active rheumatic fever in young adult white males were observed throughout the course of their illness at the Francis E. Warren Air Force Base Station Hospital in Cheyenne, Wyoming. The present report summarizes clinical studies in connection with this group of patients.

Method of Study. The diagnosis of active rheumatic fever is at times established with difficulty, especially in that group of patients who manifest only a few of the signs of the disease following a streptococcal infection. In the present study the criteria of Jones[21] were slightly modified and used as a guide in establishing a diagnosis. Migratory polyarthritis and carditis were considered as major manifestations of active rheumatism. Carditis could be established by the presence of a distinctly abnormal electrocardiogram or by the development of cardiac enlargement, pericardial friction rub, heart failure, or a significant new murmur. Chorea and subcutaneous nodules, 2 signs which are also listed as major manifestations, were of little import in view of their rare occurrence in this age group. Minor manifestations considered were fever, elevated erythrocyte sedimentation rate, arthralgia or mono-arthritis, suggestive but not marked electrocardiographic changes, erythema multiforme or marginatum, and unexplained pneumonitis or peritonitis. Each case was, of course, considered in an individual manner for purposes of diagnosis. For

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the cases presented in the following analysis, the minimal requirements were the presence of two major manifestations or a combination of one major and at least two minor manifestations.

On admission a complete history and physical examination were recorded on each patient. Special wards were established to care for the rheumatic fever cases so that intermingling with other diseases was avoided. In view of the previously published opinion[7,36] that *absolute* bed rest is not necessary and may actually be harmful, patients were placed on modified bed rest. Recreational and occupational activities were permitted in bed provided no undue exertion was involved. Patients not incapacitated by the illness were allowed one visit to the bathroom in a wheel chair daily. By means of personal discussions and group lectures on the nature of their disease, attempts were made to allay apprehension and gain full co-operation. No ambulation or other significant activity was permitted until all physical and laboratory abnormalities had become and remained normal for a period of two weeks. They were then gradually allowed out of bed according to a constant plan over a period of about two months. All patients were given a high caloric diet. Rectal temperatures were obtained every 4 hours during the febrile phase of the illness and every 6 hours for the remainder of the hospital course. Body weight was charted on admission and once weekly thereafter. Blood pressure was recorded once a week. Standard and chest CF-4 lead electrocardiograms were taken daily during the entire active phase of the sickness and 3 times a week throughout convalescence. An erythrocyte sedimentation rate was obtained 3 times weekly while elevated, and once a week for the remainder of hospitalization. A complete blood count, including a differential count, was ordered once weekly and an additional white blood count was done twice weekly during the acute phase. Teleoroentgenograms of the chest were taken whenever possible on admission and were repeated as indicated in order to follow the heart size or pulmonary lesions. Throat cultures and blood for serologic studies were obtained on admission and at 1–2 week intervals throughout the hospital stay. Cardiac fluoroscopy was performed on all cases in which there was valvular heart disease at the time of discharge.

All cases were observed daily by the same

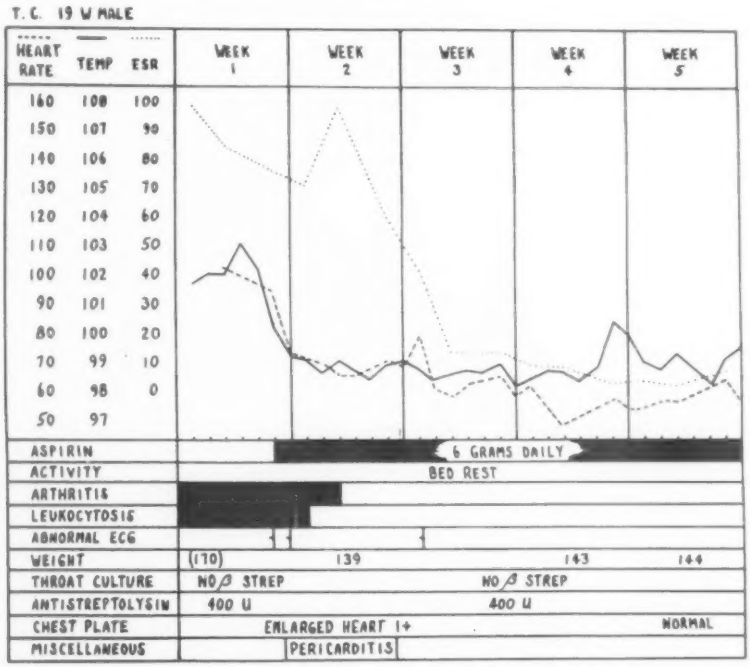

FIG. 1.—Chart demonstrating the early phase of the hospital course of a patient suffering from acute rheumatic fever.

physicians and were retained in the same hospital throughout the course of their immediate illness and convalescence.

In the course of this study, a controlled evaluation of aspirin therapy was carried out. In view of recent reports[17,41,42] that massive salicylate therapy does not alter the basic disease process beneficially, and because of the discomfort and danger accompanying massive treatment, moderate doses were used. Aspirin was administered rather than sodium salicylate because of the less frequent gastric irritation and intolerance with this agent. No sodium bicarbonate was given. The treated patients received 6 grams of aspirin daily in divided doses. No symptoms or signs of salicylism developed on this regimen. The control patients received no drugs other than codeine for the relief of pain. In order to avoid undue suffering, a provision was made whereby a control patient could be eliminated from the study and treated in the usual fashion should his symptoms so indicate. This was found necessary, surprisingly enough, in only 5 cases.

Summary charts of each patient's hospital course were constructed. Fig. 1 is an example of the first page of such a chart.

Results. History. The patients in this study were obtained from a military population and were therefore a selected group in relation to age and sex. All cases were males. No patient over 30 or under 17 years of age was included in the analysis. Ninety-two percent of the cases fell into the 17 to 21 age group. No case in the colored race was considered. A review of the histories in relation to the home state of each patient revealed no predominance of cases from any certain geographical locality. A past history of rheumatic fever or chorea was obtained in 24% of the cases. Fourteen percent knew of another member of their family who had suffered from rheumatic fever. Thirty-one percent of the patients gave a history of having had their tonsils removed. A simultaneous study in the same hospital revealed that 29% of a non-rheumatic population had had a tonsillectomy[8]. Seventy-eight percent of the cases could recall a significant recent upper respiratory infection at the time of admission for rheumatism. The infection occurred from 6 to 40 days prior to the onset of the rheumatic symptoms, with a mean time interval of 19 days between the respiratory episode and the rheumatism. The nature of the respiratory disease complaints was varied but most commonly consisted of a sore throat lasting 3 to 4 days, usually accompanied by feverishness and malaise.

Complaints. So far as the symptoms of rheumatic fever were concerned, the most consistent and prominent complaint was that of joint pain. All except 4 of the cases appeared with this as the presenting symptom. Anorexia, weakness, weight loss, myalgia, fatigability, and malaise were other common but less specific symptoms. Epistaxis was frequently encountered but was of doubtful significance in view of its spontaneous occurrence at this high altitude. Complaints referable to the cardiovascular system were notable by their rarity. Gastrointestinal and pulmonary symptoms were encountered in occasional cases.

Arthritis. Ninety-one percent of the cases had objective changes of inflammation (local heat, erythema, or swelling) about one or more joints. The arthritis was quite variable in both its nature and course. In the great majority of instances the discomfort produced by the joint inflammation was severe and incapacitating. Subjective complaints of pain and tenderness commonly preceded the appearance of objective changes by several hours. Local heat was the most frequent physical sign encountered. Erythema appeared about involved joints in approximately one-half of the cases. The initial arthritis was commonly in a large weight-bearing articulation. In 44% of the patients the first joint inflamed was a knee, and in 30% the initial arthritis appeared in an ankle. Though the larger joints were more commonly affected, examples of in-

flammation of unusual and small joints (temporomandibular, sternoclavicular, metatarsophalangeal) in a few cases attested to the fact that any articulation may suffer in the rheumatic process. In the usual patient the severity of the constitutional symptoms and signs was proportional to the degree of arthritis. In rare cases what seemed to be severe joint involvement was not accompanied by discomfort, fever, or prostration. In other uncommon instances the reverse was true with minimal arthritis and severe constitutional disability. Migration of the arthritis occurred in 94% of the cases and was somewhat variable in its nature. As a rule a single joint remained inflamed for 4 to 6 days with migration to 2 to 3 joints in the entire course of the arthritis. Occasionally joint involvement was extremely fleeting with a duration of only a few hours. In other uncommon instances a single joint remained inflamed for prolonged periods of time (weeks) so as to bring about suspicion of rheumatoid changes in the minds of the observers. No pattern of sequence was noted to be more common than any other in the migration.

In addition to the diffuse periarticular tissue involvement of the arthritis process, specific inflammation of the tendon sheaths about the area was frequently noted. This rheumatic "tendonitis" was evidenced by objective

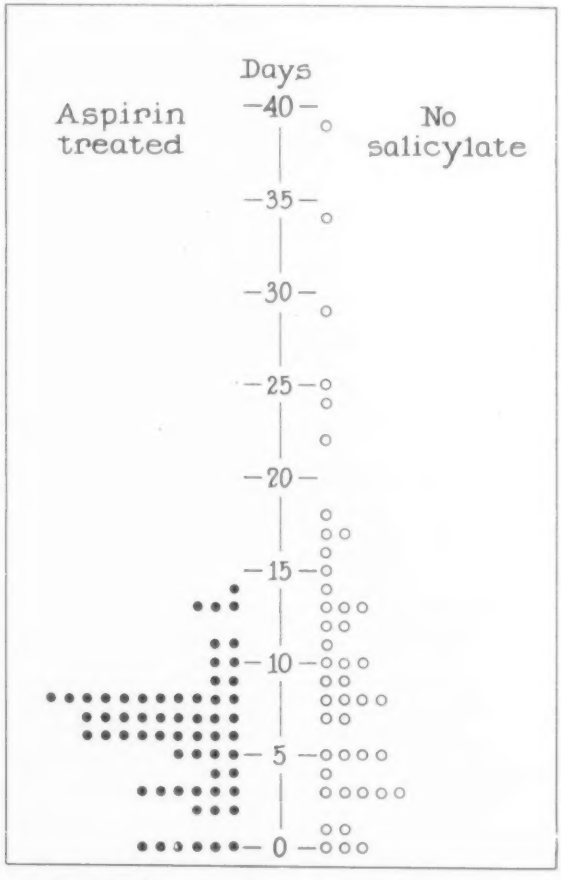

FIG. 2.—Duration of arthritis in 109 patients.

signs of inflammation along the course of tendons in approximately one-third of the cases.

Fig. 2 illustrates, in scatter-graph fashion, the duration of the arthritis. In the group of patients who did not receive aspirin the duration of the arthritis is seen to be quite variable. It is of interest to note, however, that the arthritis in this control group most commonly subsided spontaneously during the second week of the illness.

TEMPERATURE. Fever was present in 98% of the patients. A patient was not considered febrile until the temperature had exceeded 100° F. per rectum. Characteristically the day's high temperature was the one recorded in the afternoon. In the group of patients who did not receive aspirin, the temperature usually rose gradually over the course of 5 to 6 days and then returned to normal in a similar fashion. Abrupt changes in temperature were seen only in those cases treated with salicylates. Fig. 3 presents the duration of fever in the treated and control groups. The variability, the mean duration without antipyretic medication, and the influence of aspirin are self evident in this scatter-graph.

MURMURS. In view of the fact that

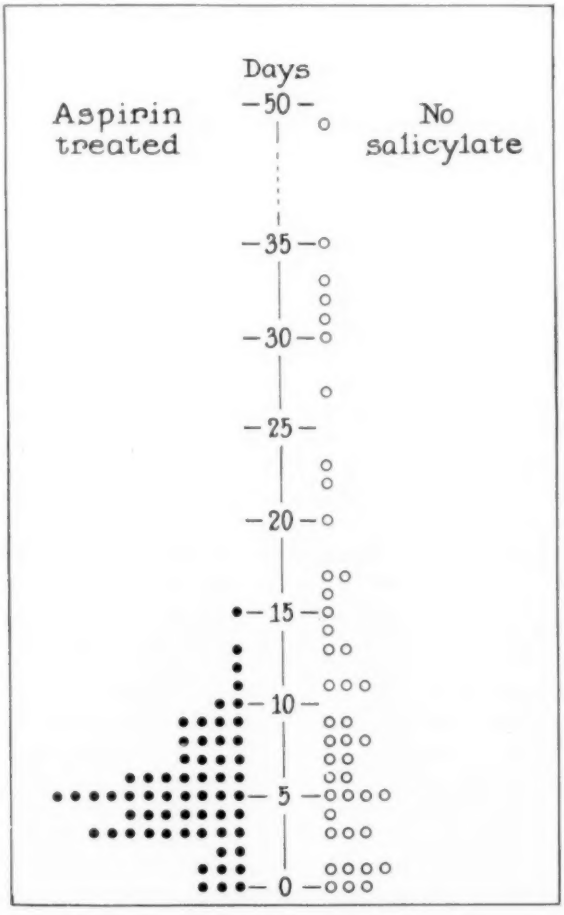

FIG. 3.—Duration of fever in 109 patients.

functional heart murmurs are frequently encountered in conditions associated with fever, anemia, and altered cardiovascular dynamics, murmurs were evaluated only after repeated and prolonged observation. Only murmurs having the characteristics of those produced by organic valvular lesions and only those murmurs persisting over a period of months were classified as significant murmurs in the final tabulation. Seven of the patients had organic murmurs on admission to the hospital, and in all but one of these there was a past history of rheumatic fever. The old heart murmurs became notably worse or significant new murmurs appeared in 19 cases. As expected, the murmur of mitral insufficiency developed most frequently. This consisted of a moderate or high-pitched blowing apical systolic murmur which was often transmitted into the left axilla. Such a murmur was noted in 15 cases. Aortic insufficiency was the next most frequent lesion to become manifest. This developed in 11 cases and was characterized by a high-pitched, often faint, blowing early diastolic murmur heard best along the left sternal border in the 3rd and 4th intercostal spaces with the patient leaning forward in respiratory expiration. That this lesion was temporarily a benign one was indicated by the fact that in none of these 11 patients was the pulse pressure altered to abnormal levels. The typical murmur of mitral stenosis developed and persisted in 2 cases. This was a low-pitched rumbling mid- or late-diastolic murmur which was often heard with difficulty and was best heard over the point of maximal impulse with the patient in the left decubitus position.

The time of appearance of the organic heart murmurs in the course of the illness varied with the type of murmur. The systolic mitral murmurs usually became evident during the acute phase with subsequent alteration in nature but with fixation and persistence after about the third month. The diastolic murmur of aortic insufficiency was commonly first heard during the 3rd and 4th month of hospitalization. It is possible that the late appearance of this murmur and the special measures necessary for its detection are factors explaining the lower incidence of its development recorded in previous studies. The relatively infrequent occurrence of the murmur of mitral stenosis is in all likelihood explained by the brevity of the period of observation in relation to the progressive pathological changes leading to this condition. Suffice it to say that the observations reported here should serve to emphasize the frequency of development of insufficiency of the aortic valve as a result of the rheumatic disease process in young adult white males. From the sums of the figures presented above, that is, a total of 28 new murmurs in 19 patients, it is evident that multiple valvular lesions in the same patient occurred frequently. Though 90 of the 109 cases escaped with no murmur at the end of the period of observation, which averaged 8 months, it is of course possible and even probable that many of these patients will develop murmurs with the passage of time[3,22].

The so-called functional murmurs heard so often during the acute stage of rheumatic fever varied widely in quality, intensity, and duration in this series of patients. Apical systolic murmurs which had been loud, rough, and high-pitched disappeared completely during ensuing observation. Though diastolic murmurs are said to be rarely of functional origin, many apical diastolic murmurs were heard transiently during the acute stage. In only 1 instance did an aortic diastolic murmur disappear and remain inaudible during the following months of observation.

HEART SIZE. In this age group and sex, severe cardiac enlargement and heart failure are said to be uncommon[6,38]. Twelve cases in this series developed cardiac enlargement of a distinct degree evidenced by increased heart size on the teleoroentgenogram. Only 2 instances of cardiac decompensation were seen and in both of these the failure was relatively mild.

HEART RATE. The occurrence of sinus bradycardia early in the course of active rheumatic fever has been previously reported[1,9,14,16,18,26,43] but is not widely recognized. Fifty-eight percent of the patients in this series developed sinus bradycardia as shown electrocardiographically during the first 5 weeks of their illness. A typical heart rate curve pattern was frequently observed. This consisted of sinus tachycardia during the febrile phase followed immediately by relative or absolute bradycardia lasting 3 to 4 days. This was in turn followed by a return of the heart rate to normal or elevated levels. The incidence of this bradycardia was not related to a past history of rheumatism, the severity of the attack or the therapy used, but did follow closely subsidence of fever. Those patients who manifested this period of sinus bradycardia had a more favorable short-term prognosis in relation to duration of the attack but were still susceptible to the development of organic heart damage.

HEART RHYTHM. The cardiac rhythm observed in these cases during the acute stage was for the most part regular sinus rhythm. In approximately one-third of the patients a diastolic gallop was evident. Prominent sinus arrhythmia was noted in one-fourth of the cases during the acute phase, often in association with electrocardiographic evidence of myocarditis. This would seem to indicate that the presence of sinus arrhythmia during active carditis is not uncommon. Other types of arrhythmia were rarely seen, including intermittent heart block, auricular fibrillation, auricular premature contractions, ventricular extrasystoles, and pulsus alternans.

PERICARDITIS. Pericarditis manifested by an audible friction rub was present in 14 cases. Pericarditis was seen in the most severe cases and was usually accompanied by cardiac dilatation and/or pericardial effusion. In no case was the amount of pericardial effusion large. Pericarditis appeared during the acute phase of the illness and varied in duration from 1 to 20 days. Most commonly the friction rub lasted about 1 week. It was disappointing to note that only 1 of these 14 cases with unmistakable to-and-fro friction rubs presented the classical electrocardiographic picture associated with pericarditis.

SKIN LESIONS. The skin lesions accompanying acute rheumatic fever are many and variably specific[4,24,25]. Erythema marginatum and erythema annulare rheumaticum are commonly considered to be characteristic of the disease. Five examples of erythema marginatum were encountered in this series of cases. The appearance of this lesion was not constantly associated with any particular phase of the illness, but it was noted to appear most often (3 cases) during the latter part of the acute phase. The duration of the lesions of erythema marginatum varied from a few hours to 3 weeks. In 2 cases this rash presented lesions which were migratory and polycyclic in this migration. In 1 instance erythema marginatum appeared after institution of aspirin therapy, and in 2 other cases the rash was apparently uninfluenced by salicylate treatment. Petechiae were observed in 3 cases during the acute stage of the disease. In all of these, the various tests for hemorrhagic tendency were normal except for the capillary permeability tests, indicating a prob-

able vascular origin for the extravasations[24]. Many of the patients developed fleeting erythematous lesions which could not be classified accurately. One case manifested erythema multiforme at the time of admission to the hospital. No examples of subcutaneous nodules were found despite daily search for them in each patient.

Weight. Weight loss was one of the most constant features of the illness. Over 90% of the patients had lost at least 10 pounds in relation to their normal body weight by the second week of hospitalization. The amount of weight lost ranged from a few to over 40 pounds. The average weight loss was 19.4 pounds. Return of appetite and gain in weight were commonly concurrent with early signs of recovery.

Other Complications. No chorea was present in this group of patients.

Rheumatic pneumonia[11,15,32] is for the most part a diagnosis of exclusion. Eight cases in this series developed pneumonitis not attributable to any cause other than the rheumatism. The pneumonia was observed only in the most severe cases and during the acute phase of the illness. The pneumonic lesions were not accompanied by any respiratory symptoms. The lung infiltration persisted for 4 to 12 days and was unilateral in every instance. In addition to these cases with pneumonitis, 6 of the patients with cardiac enlargement demonstrated compression of the left lower lung producing abnormal physical signs below the left scapula.

The occurrence of abdominal findings in acute rheumatic fever is well recognized[2,35]. Two patients in this series had signs of peritonitis as prominent features of the acute rheumatism. Differentiation from true intra-abdominal disease is admittedly difficult. That the latter may occur is illustrated by the fact that two other patients were operated upon during their hospital course, one having a gangrenous retrocecal appendix and the other an ileocecal intussusception. Fortunately these complications both appeared during convalescence and were unaccompanied by signs of a rheumatic relapse, thus rendering differentiation from rheumatic peritonitis somewhat easier.

Course. As a rule the total illness ran a benign course. In one patient moderate activity had been resumed after only 9 weeks. In the most protracted case, the patient was not allowed up for 62 weeks. The mean time elapsed before a patient was up at liberty on the ward was 21 weeks. In none of the cases was there a fatal outcome. Nineteen of the patients had illnesses of a polycyclic pattern. It was of interest to note that 15 of these had received aspirin. It was common to observe a clinical relapse appearing within 2 to 7 days following discontinuation of the salicylate. Though this is usually explained as continuing activity which has been suppressed during the aspirin treatment, such is not necessarily the case. The fact that 13 of these 15 "aspirin-withdrawal" relapses were mild and self-limited without reinstitution of salicylate treatment suggests some sort of an escape phenomenon since it is unlikely that true activity should subside at the same relative time in such a large group of cases.

Laboratory Findings. Sixty-seven of the patients had a white blood count above 12,000 during the acute phase of their illness. The duration of the abnormally high leukocyte count ranged up to 3 weeks. A mild leukocytosis (12,000 to 15,000) was the rule.

Elevation of the erythrocyte sedimentation rate was present in every one of the patients. The sedimentation rates were commonly high, averaging 90 mm. per hour (Westergren) at their peak. As a rule the height of the sedi-

mentation rate was proportional to the degree of arthritis and fever. The return of the sedimentation rate to normal was usually a gradual and regular process. The rapidity with which this return to normal was accomplished varied widely from 2 weeks to over 6 months. Fig. 4 shows the duration of elevation of the sedimentation rates in the aspirin-treated and control patients. In the untreated group, one sees that the sedimentation rate most commonly returned to normal after 5 to 7 weeks.

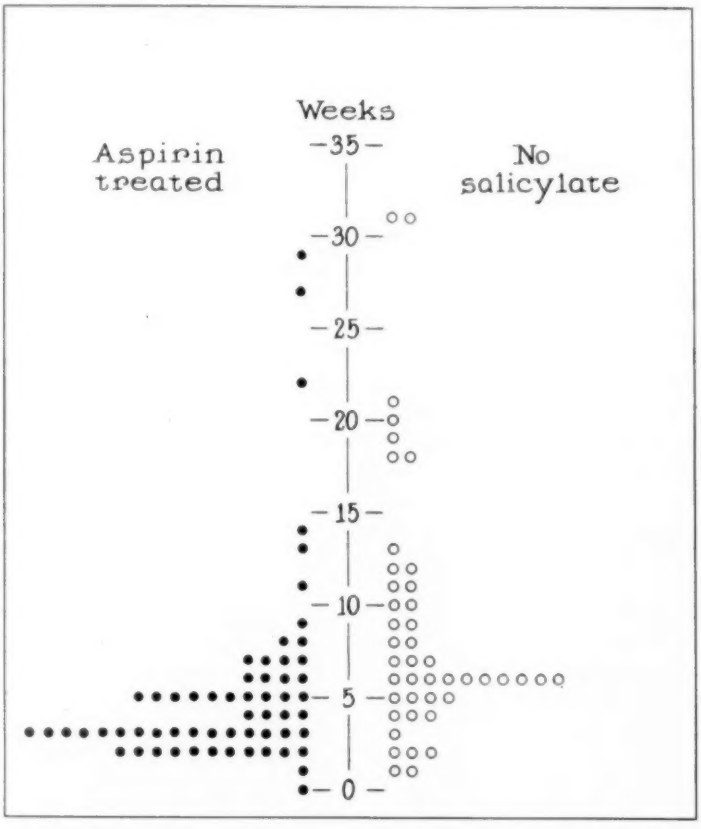

FIG. 4.—Duration of elevation of erythrocyte sedimentation rate in 109 patients.

Antistreptolysin "O" titers were performed by a modification of the method of Hodge and Swift[19]. Considering any titer over 150 units elevated, an elevated antistreptolysin level was found in every patient in the series except 1. In 71% of the cases the highest antistreptolysin titer was 400 units or greater. A significant rise in titer (2 tubes or more) was demonstrated in approximately one-third of the group. It was noted that the antistreptolysin level began to fall gradually after 1 to 2 months. The rate of fall was variable, and in some cases the titer had not reached normal values after over a year of observation.

STREPTOCOCCIC INFECTION. It is now generally accepted that rheumatic fever is a complication of infection with the beta hemolytic streptococcus[5,23,30,33,34,40]. During the period of this study the rate curve of rheumatic fever con-

formed roughly to that of streptococcal disease with a 1-month lag. The incidence of streptococcal infections of the upper respiratory tract was strikingly high. Approximately 3 cases of rheumatism resulted from each 100 cases of hospitalized streptococcal illness. This would seem to indicate that the widely publicized high rate of rheumatic fever in the Rocky Mountain Area may be merely a reflection of the frequency of streptococcal infections under certain conditions in this region.

Thirty-eight of the patients in this study were observed during the respiratory infection which preceded the rheumatism. Thirty-two of these had a positive throat culture for group A streptococci during this pre-rheumatic infection. The streptococci, where cultured, were typed by the method of Lancefield[39]. Predominant types were 5, 14, and 24. During most of the present study, a concurrent investigation of the influence of penicillin in the treatment of acute streptococcal pharyngitis was in progress. As reported by Denny *et al.*[8], it was found that penicillin treatment of streptococcal pharyngitis prevented the subsequent occurrence of rheumatic fever. This is reflected in this rheumatic fever series by the fact that all but 2 of these 32 patients came from the control group which received no penicillin for their acute respiratory infection. In the analysis of this group of patients observed prior to development of rheumatic fever, it was found that in 13 of those with positive throat cultures for streptococcal infection, the same type of beta hemolytic streptococcus remained in the pharynx at the time of admission for rheumatic fever. In 12 instances the throat culture at the time of admission for rheumatism revealed a new streptococcal type to be the inhabitant. In 7 cases the throat culture had become negative for group A streptococci. In view of the fact that this study was performed in a locale rampant with streptococcal disease, it was difficult to draw any conclusions from the above information. Suffice it to say that evidence of a recent streptococcal infection was present in almost every case, and in many instances there was evidence suggesting multiple streptococcal infections.

Electrocardiograms. Studies of the electrocardiographic changes observed in acute rheumatic fever are too numerous to list. Two of the more recent discussions of the subject[12,31] emphasize points of importance. No electrocardiographic change is absolutely specific for rheumatic fever. First degree heart block, ST segment changes, and T wave inversions are all characteristic but may also be found in other conditions. Divergence of findings in the literature in relation to the percentage of cases of rheumatic fever showing electrocardiographic changes may be attributed in part to variation in interpretation and in part to the fact that the percentage of abnormal tracings depends upon the frequency with which observations are made. In the present study electrocardiograms were recorded daily throughout the acute phase of the illness. There were 3 classes of changes which were considered indicative of carditis: 1) Heart block of various degrees with P-R interval greater than 0.21 seconds, 2) inversion of the T waves in leads I and CF-4, and 3) ST segment and T wave changes of pericarditis. There were many other findings such as changing P-R interval, shifting auricular pacemaker, lowering of the T waves, changes in the Q-T interval, and abnormalities of the ST junction, all of which were regarded as suggestive but not indicative of carditis. Using these criteria, 88% of the patients in this series demonstrated on at least one occasion a change in the electrocardiogram diagnostic of carditis. Table 1

contains a type breakdown of the electrocardiographic abnormalities. Electrocardiographic changes were usually observed during the acute stage of the illness. They were commonly transitory, but in 19% of the cases there was a residual significant change which persisted months after all other abnormalities had disappeared. The significance of this protracted electrocardiographic abnormality was not clear. There was no correlation between this finding and the severity of the illness or the appearance of valvular damage.

TABLE 1.—TYPE DISTRIBUTION OF THE SIGNIFICANT ELECTROCARDIOGRAPHIC ABNORMALITIES OBSERVED IN 93 CASES

Atrio-ventricular dissociation	12%
First degree heart block	43%
T wave inversion leads I and CF-4	16%
ST segment elevation and T wave inversion	3%
First degree heart block plus T wave inversion	26%

TABLE 2.—THE EFFECT OF ASPIRIN THERAPY UPON THE DURATION OF THE ATTACK AND THE APPEARANCE OF HEART DAMAGE

	Aspirin Treated	*No Salicylate*
Time in hospital until up at liberty (mean in weeks)	21.5	22
Development of significant persistent heart murmurs	9 (15%)	8 (18%)

ASPIRIN THERAPY. A comparison was made between patients given moderate doses of aspirin and those receiving no salicylate. After eliminating 5 of the patients who were placed on aspirin because of the severity of their symptoms and who were not, according to the code, to receive aspirin, there were 60 patients who received aspirin and 44 who did not. Control in case selection was obtained by utilization of the patient's Air Force serial number. If the last digit of this figure was odd, he was given no salicylate; if even, he was placed on aspirin. The comparability of the two groups in terms of severity of the illness was as follows: The average maximum fever (prior to therapy) in the aspirin-treated group was 102.9° F., while in those not given salicylates it was 103.1° F. The mean highest sedimentation rate was 91.7 mm. per hour in the aspirin-treated group and 88.9 mm. per hour in the controls. Figs. 2, 3, and 4 illustrate the effect of aspirin on the course of the disease in terms of duration of arthritis, fever, and elevated erythrocyte sedimentation rate. That aspirin administration probably had some effect is evidenced by the slight reduction in mean duration of fever and arthritis in the group of patients receiving this agent. The sedimentation rate returned to normal somewhat more rapidly in those patients who were given aspirin, but previous investigation[17,20] has shown that salicylates may bring about a reduction in the sedimentation rate *per se*. This is therefore not a clear indication of an effect on the disease process itself.

Table 2 shows that the length of time in which recovery from the immediate illness occurred was the same in the treated and control patients, and that the percentage of cases developing heart murmurs indicative of valvular damage was not statistically different in the two groups.

Summary. A review of the clinical features of acute rheumatic fever in the young adult white male is presented.

One hundred and nine cases of this disease were studied and various observations in relation to the history, physical findings, course, laboratory values, and therapy were recorded.

There was evidence of recent beta hemolytic streptococcal infection in almost every case. Migratory polyarthritis and fever were the outstanding clinical manifestations of rheumatic fever in this group. It was found that carditis could be demonstrated electrocardiographically in a high percentage of cases provided daily tracings were taken. Sinus bradycardia was found during the acute phase of the rheumatic attack with surprising frequency. Though the total disease characteristically ran a benign course, organic heart murmurs appeared and persisted in 17.4% of the cases. Mitral insufficiency and aortic insufficiency were the two predominant valvular lesions developing. Moderate doses of aspirin were probably effective in alleviating symptoms but were ineffective in shortening the course of the illness or in preventing the development of valvular heart disease.

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THE INCIDENCE AND COST OF TREATMENT OF BACTERIAL ENDOCARDITIS: A STUDY OF ALL CASES OCCURRING IN METROPOLITAN WASHINGTON IN THE YEAR 1948

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As long as no therapeutic measures were successful in the treatment of bacterial endocarditis, the incidence of the disease was not given much thought. Cases of this disease were listed in the group of illnesses in which death was inevitable and thus dismissed. During this period, moreover, no reasonable estimate could be made regarding the average cost of treatment in a case of endocarditis since the cost varied widely from case to case, depending upon whether treatment other than symptomatic was tried or whether the family and the physician accepted the diagnosis as sealing the patient's death warrant.

Since penicillin has been shown to bring about recovery in approximately two-thirds of the patients treated and other antimicrobial agents give promise of raising the recovery rate still higher, it has become important to determine whether we are at present utilizing our therapeutic measures as fully and as efficiently as possible, and, if not, what can be done about it. Accordingly, it is necessary first to determine for the disease its frequency of occurrence, its fatality rate, the loss of time because of it, and its cost of treatment. In the present paper we are presenting the results of such a study for Metropolitan Washington.

Plan of Study. The records of patients who had been admitted to hospitals in the Washington Metropolitan area during the year 1948 and who lived in the District of Columbia, in Montgomery or Prince Georges Counties in Maryland, or in Arlington or Fairfax County or Alexandria in Virginia, were examined by us.

The diagnosis of endocarditis may not be made in persons with bacteremia unless the physician is on the lookout for, and is aware of the significance of, the sudden appearance of a heart murmur or a change in an existing heart murmur. For this reason, patients with rheumatic heart disease may die with superimposed bacterial endocarditis without the latter condition being detected during life. Furthermore, when acute bacterial endocarditis develops during the course of an acute bacteremia, the endocarditis may not be diagnosed during life unless the significance of a murmur is recognized. Accordingly, we paid particular attention to patients with rheumatic heart disease who were febrile and to all patients with bacteremia whether suspected of having bacterial endocarditis or not. If, in our opinion, the evidence was sufficient to justify a diagnosis of endocarditis, the case was included in the present series. Thirty-three patients were found to fit into this category (Table 1); 10 of these either had been treated or had been seen in consultation by one of us (H.F.D.). The diagnosis was made on the basis of the physical findings plus positive blood cultures in the case of 26 patients, while in 7 patients the diagnosis was not made with certainty during life but endocarditis was found at autopsy. An additional patient was a resident of another state who had been sent to one of the Washington Armed Forces hospitals for treat-

ment. His case was not included in the series. Two other patients with endocarditis were treated in Washington hospitals during 1948 but were not included in the series because treatment had been started in 1947.

It seems quite certain that all the patients in this area with endocarditis or suspected endocarditis were admitted to a hospital at some time during the course of their illness. Furthermore, it is unlikely that any patients were sent to hospitals outside of this area, since all of the counties and Alexandria city are within the District of Columbia medical service area[2] except the northern part of Montgomery County, which is predominantly rural and contains only a small part of the population of Montgomery County.

and 285,988 Negroes. If we use these figures, we find that there was approximately 1 case for every 42,000 white persons and 1 case for every 26,000 Negroes. There were 23 cases of endocarditis in males as compared with 10 in females. Since there were slightly more females than males in the area, it is evident that the proportion of males with endocarditis was much greater than the proportion of females with this disease.

Death occurred in 20, or 61%, of the patients. Eight of the patients were

TABLE 1.—INCIDENCE OF ENDOCARDITIS IN METROPOLITAN WASHINGTON, D. C. PATIENTS WHOSE TREATMENT WAS BEGUN IN THE YEAR 1948

Population area	*Number of patients*	*Estimated population 1948*	*Incidence of Endocarditis per 100,000 population*
Metropolitan Washington	33	1,402,000	2.4
District of Columbia	27	863,000	3.1
Metropolitan Washington outside of the District of Columbia	6	539,000	1.1
Patients from area outside of Metropolitan Washington treated in Washington hospitals	1	—	—

Analysis of Cases. INCIDENCE AND MORTALITY RATE. According to the estimate of the United States Bureau of the Census[7], there were 863,000 persons in the District of Columbia on July 1, 1948 (Table 1). Since there were 27 patients with endocarditis from the District proper, there was one case for every 32,000 inhabitants, or an incidence of 3.2 per 100,000. The population of Metropolitan Washington was estimated to be 1,402,000. There were 33 patients with endocarditis from the entire area, or 1 in 42,000 inhabitants, an incidence of 2.4 per 100,000.

Twenty-two of the patients were white and 11 were Negroes. Estimates of the number of white persons in the Metropolitan area are not available for 1948, but in 1947 there were estimated to be 919,232 white persons

not given specific treatment for endocarditis since the diagnosis was not made before death. If these patients are excluded, 12, or 48%, of the remaining 25 patients died.

DURATION OF ILLNESS AND OF HOSPITALIZATION. The amount of time spent in the hospital varied for different patients from 3½ hours to 207 days, the average duration of hospitalization being 41 days. If the patients who died are excluded, the time in the hospital averaged 68 days and varied from 7 to 207 days.

It was impossible to determine the total amount of disability experienced by the patients since the time spent in convalescence could not be ascertained. A history of the illness before admission to the hospital was available, however, for 29 of the patients. The average duration of their illnesses

from the time of onset until discharge from the hospital averaged 87 days with extremes of 6 to 444 days. If we add 30 days as a reasonable minimal period of convalescence before a patient would be likely to return to his customary duties, the average duration of total illness per patient would be 117 days.

Amount of Penicillin Used. Penicillin was given to 25 patients who were diagnosed during life as having endocarditis. A total of 4,288,250,000 units of crystalline penicillin was given to 19 patients and a total of 162,250,000 units of repository penicillin to 10 patients, 4 of whom also received crystalline penicillin. The average amount of penicillin of both kinds administered per patient was 178,020,000 units.

Cost of Diagnosis and Treatment. The costs have been analyzed only in the case of the 13 patients who were in private hospitals and whose illness was diagnosed during life. They are listed in Table 2 and represent the costs paid by the patients. The average stay in the hospital for the patients who recovered was 34.8 days and the average cost per patient was $601.61, which included the cost of hospitalization, antibiotics and other drugs, and laboratory and other fees, but did not include the services of the private physician.

The average stay in the hospital for the patients who died was only 17.4 days. The average daily cost of drugs and of laboratory services was somewhat higher for this group, however, so that the average total cost per patient was $534.49.

Sickness Insurance. Among the 16 private patients, 10 had no insurance which could be applied to cover the costs of medical care. Three were subscribers to Group Hospitalization, Incorporated, which is a group plan for hospitalization insurance sponsored by the medical societies and hospitals of the District of Columbia. A large part of the cost of hospitalization and of the laboratory fees and all of the charges for antibiotics and drugs were paid for these patients by Group Hospitalization for the first 4 weeks and one-half of the cost of hospitalization for an additional 30 days. One patient was a member of Group Health Association, a cooperative group organization which renders complete medical care in the majority of illnesses to its members on a prepayment basis. All of this patient's medical expenses, including physician's fees, were paid by this association.

None of the 17 patients who were

TABLE 2.—COST TO PRIVATE PATIENTS OF THE DIAGNOSIS AND TREATMENT OF ENDOCARDITIS

	Cost to all patients		*Cost to patients who recovered*		*Cost to patients who died*	
Item	*Total for 13 patients*	*Average per patient*	*Total for 8 patients*	*Average per patient*	*Total for 5 patients*	*Average per patient*
All costs	$7821.03	$601.61	$5148.58	$643.56	$2672.45	$534.49
Cost of hospitalization	3629.95	279.07	2901.70	362.71	728.25	145.65
Cost of Antibiotics and other drugs	2977.95	229.07	1662.95	207.87	1315.00	263.00
Laboratory fees	1026.40	78.95	413.40	51.67	613.00	122.60
Other costs	186.73	14.36	170.53	21.31	16.20	3.24
Number of days of hospitalization	365	28.1	278	34.8	87	17.4

cared for at public expense had any form of sickness insurance.

Discussion. Very few data are available in the literature on the incidence of bacterial endocarditis in the general population. The number of deaths reported in 1948 as due to bacterial endocarditis in the United States was 713, representing a mortality rate of 0.5 per 100,000 population[3]. This rate is undoubtedly lower than the actual mortality rate from this disease because of failure on the part of physicians to diagnose some cases of the disease and also because some cases probably were reported under other disease headings.

Hedley[4] in a study of the mortality from rheumatic heart disease in Philadelphia during the year 1936 found that there were 86 deaths from subacute bacterial endocarditis. Since the population of Philadelphia is estimated by Hedley to have been 2,028,511 at that time, this would be equivalent to a mortality rate of 4.2 per 100,000 population. Those cases were excluded, however, where endocarditis was superimposed upon congenital cardiovascular defects or associated with septic conditions. There are several discrepancies between Hedley's figures and ours: 1) We have included all forms of bacterial endocarditis, acute and subacute, whether superimposed upon rheumatic heart disease or not. 2) We have included only the residents of the area studied. Patients sent to hospitals or to physicians in Metropolitan Washington from elsewhere have not been included. 3) We included only the cases wherein the disease began (or rather wherein the first treatment was given for the endocarditis) in the year 1948. In Hedley's data there are undoubtedly many cases in which the disease began in the preceding year. 4) Since the death rates from acute rheumatic fever as well as from heart disease of rheumatic origin are declining[3], and since the septic infections which are sometimes followed by acute endocarditis are being much better controlled with the advent of the antibiotics, it is possible that the over-all incidence of endocarditis was lower in 1948 than it was in 1936.

The Metropolitan Washington area has certain advantages for the study of the frequency of occurrences of bacterial endocarditis: 1) It is a combined urban, suburban, and rural area in which all of the inhabitants have ready access to a center where complete medical care is available. 2) The area is large enough to be representative and yet small enough to be surveyed easily. 3) Since the quality of medical care is good throughout the area, all of the cases of endocarditis occurring are likely to be discovered. 4) It is unlikely that patients would be sent out of the area for the treatment of endocarditis. For these reasons, we believe that our figures closely approximate the true incidence of endocarditis in the population.

If the same incidence, 2.4 per 100,000 persons, which we found in Metropolitan Washington held true for the entire United States, there were approximately 3400 cases of the disease in the entire country in 1948. If the case fatality rate for these was the same as for the area studied, namely, 61%, approximately 2000 persons died of this disease in the United States during 1948. Again, if we apply our figures to the United States as a whole, this would mean 139,000 days of hospitalization for endocarditis during 1948 and approximately six hundred trillion units of penicillin administered. The cost of penicillin required for the treatment of all the patients with endocarditis during a given year, at present-day wholesale prices, would be about $500,000.

The question arises as to whether it might not be possible for state and

local governments to pay for the antibiotics used in those instances in which the patient is unable to pay for them. Such programs could be organized in the same way as the pneumonia control projects which were active in a great many states and cities when antiserum was the treatment of choice for pneumococcic pneumonia[1,5,6]. This could be done by establishing a list of consultants, one of whom would examine a patient with endocarditis at the request of the patient's physician if the patient were unable to pay for the necessary antibiotics. If the consultant concurred in the diagnosis, he would recommend a dose of the antibiotic which would then be released by the Health Department for use in that particular case. The patient would remain under the care of his private physician during the treatment.

In addition to alleviating financial hardship for many patients with endocarditis, this method would have the advantage of improved diagnosis of endocarditis in general, because the private physician would feel free to call a consultant when he needed one. Secondly, many patients would be able and willing to pay the costs of hospitalization and the physician's fees if the cost of the drugs (which amounted to 39% of the total cost in our series) was paid from other sources. Furthermore, as the skill of the profession in the treatment of endocarditis improved and as our methods of administration were better controlled (especially with the use of the repository forms of penicillin), it is quite likely that many patients could be treated at home, thus dispensing with the cost of hospitalization altogether.

It is interesting to consider the case fatality rate observed in the patients surveyed. The fatality rate of 61% is higher than the rates which have been reported in the literature for patients with endocarditis treated with antibiotics. The reports in the literature, however, are composed mostly of cases from medical centers where particular attention has been given to the treatment of endocarditis; they do not include patients who died before the diagnosis was made, and they do not ordinarily include patients with acute bacterial endocarditis. Our cases, on the other hand, include patients treated in both large and small hospitals and by general physicians as well as specialists. Furthermore, all patients with endocarditis were included whether treated adequately, inadequately, or untreated, and regardless of the etiologic agent. We believe, therefore, that these data more nearly reflect the true case fatality rate for endocarditis as it existed in the United States in 1948.

Summary. 1) The records of all patients with endocarditis in the hospitals of the Metropolitan Washington, D. C., area during the year 1948 were analyzed.

2) Thirty-three patients entered a hospital for the first time with endocarditis during that year, an incidence of 2.4 per 100,000. The incidence was slightly higher for Negroes than for white persons and definitely higher for males than for females. Death occurred in 20, or 61%, of the patients. In the case of 7 of these patients the diagnosis was not made during life.

3) The average duration of hospitalization for all patients was 41 days and the average amount of penicillin administered per patient, 178,020,000 units. The average cost per private patient (including all hospital expenses but not physician's fees) was $601.61.

4) If these figures are representative of the United States as a whole for the year 1948, there must have been approximately 3400 cases of the disease in the nation and 2000 deaths. The ap-

proximate cost of the penicillin used in the treatment of these patients would be one-half million dollars at present-day wholesale prices.

5) It is suggested that the various states and municipalities initiate programs to provide antibiotics to patients with bacterial endocarditis who cannot afford to pay for them. These programs could be set up in a manner similar to those which formerly provided serum for the treatment of pneumococcic pneumonia.

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A STUDY OF THE ANTIGEN-ANTIBODY MECHANISM IN RHEUMATIC DISEASES*†

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RHEUMATIC diseases have been considered by many investigators to be the result of an unusual form of hypersensitivity reaction[13,21,25,27,29-31,41-47,54,56,60]. There is increasing evidence that cortisone and ACTH influence the immune reaction in both animals and man[2,3,10-12,20,22-24,26,28,35,36,51,53,62]. The dramatic but usually temporary improvement in most instances following cortisone or ACTH has suggested a blocking action on the antigen–antibody mechanism and has provided clinical support for the theory of hypersensitivity. The relapses following hormone therapy have indicated persistence of the antigen in the affected areas.

Antigen. If one accepts the hypersensitivity phenomenon as basic in the pathogenesis of rheumatic diseases, the next logical step is to focus attention once again and with a clearer view upon the antigen or antigens themselves. The investigations of Swift[54], Coburn[13], and many others have revealed the undeniable relationship between the beta-hemolytic streptococcus and acute rheumatic fever. However, from the clinical point of view it has been difficult to understand why similar cardiac changes should be observed in Sydenham's chorea, rheumatoid arthritis, and rheumatic fever, when the beta-hemolytic streptococcus can be etiologically related to only one of these three diseases. It might be logical to suggest that there may be a more fundamental antigen as a common denominator in all collagenous diseases. This would be compatible with the observed clinical and pathological blending of certain aspects of this disease spectrum. On this basis the streptococcal antigen in rheumatic fever might assume a secondary rather than a primary role.

If a common antigen does exist in these diseases, it must meet certain specific criteria. The persistence of

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the antigen in the affected areas might suggest that it is a living agent, invisible in tissues. This agent should be capable of passing cell membranes and residing intracellularly in greatest concentration at the affected areas where the signs of clinical activity are most marked. It should be of low pathogenicity and behave more as a parasite than as a virulent agent. Organisms of the pleuropneumonia group (L organisms) would satisfy these criteria. Their minute size, fragility, fastidious growth requirements, and filtrability separate them from ordinary bacteria and place them in a unique group intermediate between bacteria and viruses. An "intracellular phase of L organisms" has been suggested by the work of Williams[61]. Animal strains of L organisms are known to produce arthritis in rodents[48,49,57]. The L component of *Streptobacillus moniliformis* has been extensively studied. *Streptobacillus moniliformis* is pathogenic for humans as well as for animals. Its affinity for joints in man, animals, and the chick embryo has been clearly demonstrated[5,9]. Although L organisms have been implicated in human articular diseases since 1939[6,15-18,55,58,59], few investigators have persisted in the study of their behavior and therefore our knowledge of these agents is very limited. We now know that one encounters far more difficulty with human strains than with animal strains in their cultivation and the production of antigen. Two strains of L organisms recovered from joint fluids of patients with Reiter's disease by Dr. Dienes were incapable of subculture[19]. We have had the same experience with one strain from a joint fluid and several strains from the genital tract of patients with rheumatic disease. Salaman could not subculture the "L"-like colonies isolated from cultures of *N. gonorrheae* by means of penicillin[50]. The strain which we separated from the gonococcus had the characteristics of human strains[4]. Strains which can be derived as bacterial variants from a number of organisms commonly present in humans have had the characteristics of the human strains isolated independently. Although we have pursued our studies on L organisms since 1938, we realize more must be known of their growth requirements and their nature before one can prove or disprove their possible etiological relationship to rheumatic diseases by the direct approach.

Effect of Antibiotics. IN VITRO STUDIES. Therefore we have sought an indirect approach to test this hypothesis. Recent *in vitro* studies have revealed that human L organisms are inhibited by various antibiotics as well as gold salts[8,34,38]. Penicillin and sulfonamides are known to be ineffective[4,5,14,16,17,39] Tables 1 and 2 indicate our observations of the relative order of inhibitory action of various anti-L substances. Freshly isolated strains have been more susceptible than stock strains. We have observed that the most marked inhibition has been produced by terramycin. Concentrations of penicillin as high as 51,200 units per cc. were necessary to produce any effect.

If L organisms are involved in the pathogenesis of rheumatic diseases, there should be a differential *in vivo* action related to that observed *in vitro*. One of two clinical effects might be anticipated: either clinical improvement or temporary intensification of the reactions. The latter would be comparable to the flare-up which may be observed in rheumatoid arthritis treated with gold salts[7] or in acute brucellosis treated with aureomycin[52].

CLINICAL STUDIES. During the past 2 years we have observed the effect of aureomycin, chloramphenicol, and terramycin on more than 150 subjects with various rheumatic and collagen vascular diseases. We have noted 2

different types of response. One group of patients was able to tolerate the antibiotics without appreciable side reactions or joint exacerbations. The majority of these patients have shown definite clinical improvement, not necessarily accompanied by a drop in sedimentation rate (Fig. 1). Relapses have been frequent within 4 to 12 weeks after discontinuation of the medication. Retreatment has been followed by a repetition of the response.

The other group of patients has been a difficult problem in management. As we have previously reported[7,8], exacerbations of joint symptoms occur during antibiotic therapy and have been pronounced in this group. Severity of joint flare-up was related to dosage as well as frequency of administration and the choice of the antibiotic. It became apparent that small oral doses (250 mg.) of aureomycin or chloramphenicol daily could be tolerated, and that terramycin in amounts as small as 10 mg. would frequently produce severe joint exacerbations. As little as 10 mg. of terramycin every 3 days was all that was necessary to eliminate L organisms from the prostatic secretion. We have previously reported that 250 mg. of aureomycin were sufficient to eliminate L organisms *in vivo*[7]. Management of these patients has been possible with ultimate clinical improvement by use of intermittent therapy, giving small doses every 3 days, then gradually increasing the individual dose according to tolerance. After using various dosage schedules, the most successful

TABLE 1.—INHIBITION OF L ORGANISMS BY ANTIBIOTICS (RECENTLY ISOLATED STRAIN)

	Micrograms per milliliter									
Antibiotic	*128*	*64*	*32*	*16*	*8*	*4*	*2*	*1*	*0.5*	*0.25*	*0*
Terramycin							0	2+	2+	3+	3+
Chloromycetin							0	2+	3+	3+	3+
Aureomycin						0	2+	2+	3+	3+	3+
Streptomycin						0	2+	3+	3+	3+	3+
Myochrysine		0	1+	2+	2+	1+	1+	1+	1+	1+	3+

	Units per milliliter							
	51,200	*25,600*	*12,800*	*6400*	*3200*	*1600*	*800*	*0*
Penicillin		0	2+	3+	3+	3+	3+	3+

TABLE 2.—INHIBITION OF L ORGANISMS BY ANTIBIOTICS (STOCK STRAIN)

	Micrograms per milliliter										
Antibiotic	*128*	*64*	*32*	*16*	*8*	*4*	*2*	*1*	*0.5*	*0.25*	*0*
Terramycin						0	9 colonies	2+	3+	4+	4+
Chloromycetin					0	19 colonies	2+	3+	3+	4+	4+
Aureomycin				0	2 colonies	17 colonies	2+	4+	4+	4+	4+
Myochrysine		0	1+	2+	2+	2+	3+	3+	3+	4+	4+
Streptomycin	0	2 colonies	1 colony	1 colony	2 colonies	2+	3+	4+	4+	4+	4+

	Units per milliliter							
	51,200	*25,600*	*12,800*	*6400*	*3200*	*1600*	*800*	*0*
Penicillin	0	2+	3+	4+	4+	4+	4+	4+

regimen proved to be very similar to that employed with gold salts, namely, intermittent therapy with small initial doses. The clinical response has also been very much of the same order as that noted with gold.

It is not our purpose at this time to discuss all the clinical details which have been observed and our reasons for concluding that the various antibiotics, only when employed in proper dosage, exert a favorable effect on collagen vascular diseases. It would appear far more important at the present time to note the usefulness of these agents in the exploration of the basic mechanism of rheumatic diseases. Exacerbations can now be induced at will with these antibiotics and the behavior and intimate characteristics of these diseases can be thrown into strong relief for comparative clinical and laboratory study. The exacerbation of one or several of the patient's original symptoms has been interpreted by us as an increased antigen–antibody reaction due to an induced release of additional antigen by the antibiotic. It has been of particular interest that those patients who demonstrated the greatest tendency to an exacerbation when given the anti-

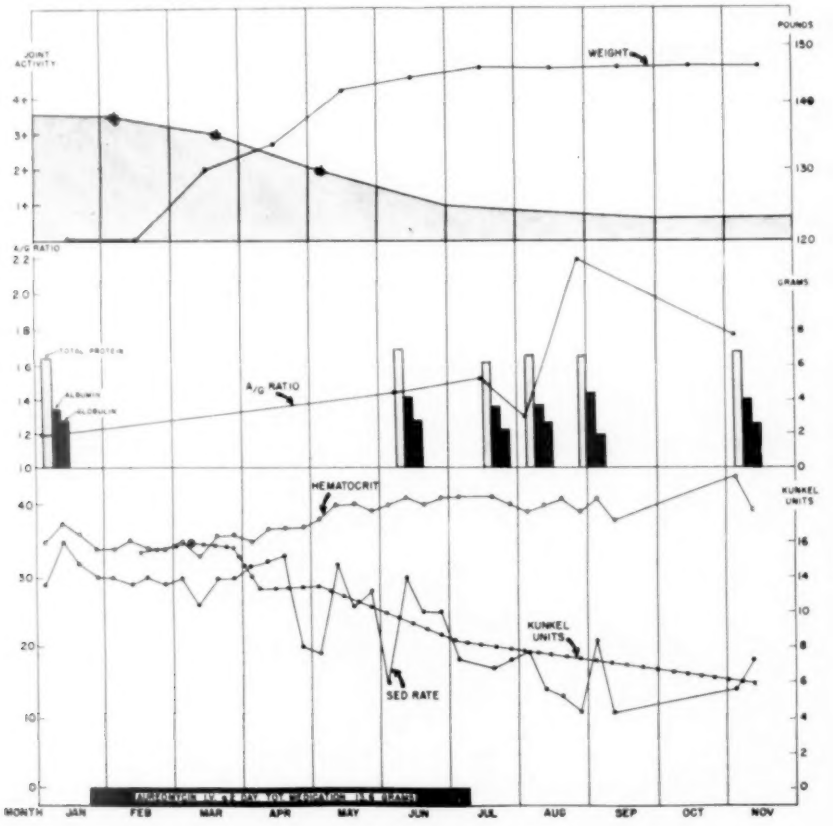

FIG. 1.—Rheumatoid Arthritis, Severe, Chronic (5 years).

* Transient exacerbation of joint pain following increase in dosage. Initial dosage, 50 mg. of aureomycin i.v. Highest single dose, 500 mg. of aureomycin i.v.

biotics were the individuals with the most abnormal serum-protein findings.

If the induced flare-up is related to an increased antigen–antibody reaction, theoretically this reaction should be blocked by simultaneous administration of cortisone or ACTH. If this could be accomplished, higher doses of the antibiotic would be possible and there would be the likelihood of more complete elimination of the antigen. Fifteen patients have been treated with cortisone and either aureomycin, chloramphenicol, or terramycin.

On this combined regimen, antibiotic tolerance could be raised considerably and much more rapidly than with the antibiotic alone. The same relative activity of these antibiotics was maintained in the presence of cortisone. For example, on a constant dose of cortisone a complete block for a given dose of aureomycin was found incomplete for the more effective anti-L substance, terramycin, even when the latter was administered in much smaller doses. Cortisone has been useful in initiating antibiotic therapy in those patients who were found to develop severe exacerbations from the antibiotics alone.

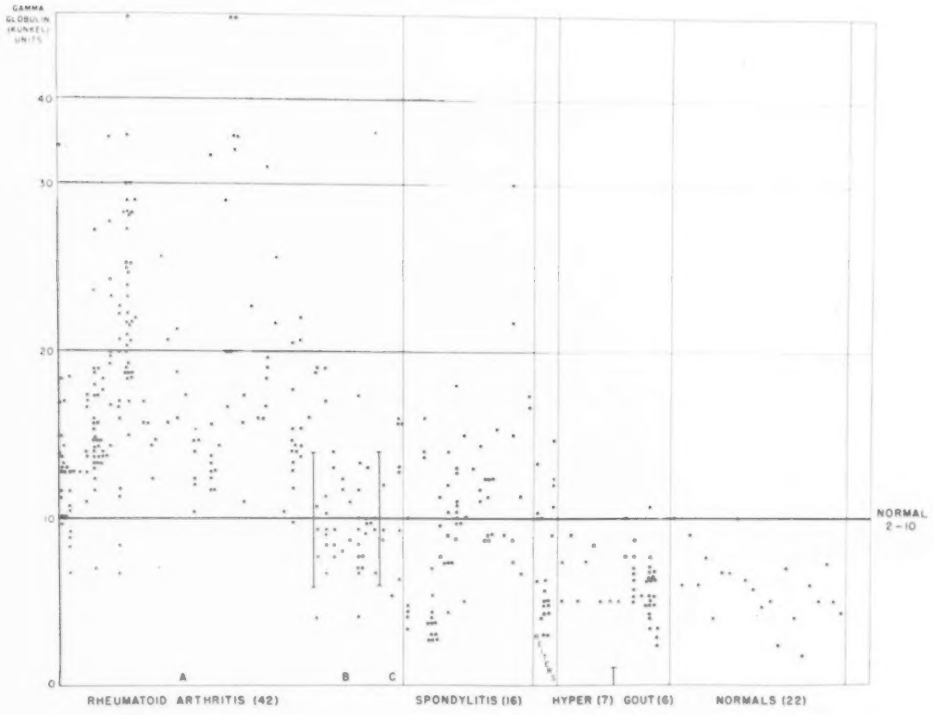

FIG. 2.—"Kunkel globulin" in various arthritic diseases.
Group A: Active rheumatoid arthritis; elevated sedimentation rate; abnormal serum proteins.
Group B: Active rheumatoid arthritis; elevated sedimentation rate; serum proteins approached normal.
Group C: Patients whose disease became clinically inactive; active state, values above normal; remission, normal values.

Serum Protein. We have been interested for a long time in the abnormal serum-protein findings in rheumatic

diseases. Electrophoretic studies have been performed before and during cortisone therapy. It has been noted that cortisone effects reduction of gamma globulin, and in most instances an elevation of the albumin fraction[1,8,32,40]. Fig. 2 emphasizes the frequency of gamma-globulin abnormalities in these diseases. We have found the Kunkel turbidimetric technique a useful method in screening patients for gamma-globulin abnormalities. We have confirmed Kunkel's observation that albumin interferes with the demonstration of gamma globulin by this method[8,33,37]. Because of this phenomenon, as well as the relatively low serum-albumin levels in severe cases and the rise in albumin levels induced by cortisone therapy, we have administered human serum albumin intravenously to individuals with active rheumatoid arthritis[8].

ADMINISTRATION OF HUMAN SERUM ALBUMIN. Electrophoretic determinations following a single injection of human serum albumin revealed a rise in the albumin and fall in the globulin fraction of the serum comparable to the effect observed with cortisone. A temporary fall in the sedimentation rate was noted in some instances[8].

Human serum albumin was administered to 8 patients with active rheumatoid arthritis. In the majority of cases there was objective clinical improvement which started within 15 minutes, with the maximum effect in 1 hour. This response was manifested by decrease of joint pain and swelling and/or increase of mobility. This improvement lasted 6 to 8 hours, although in some instances there was a consistent feeling of well being which persisted for several days. The amount of albumin required to produce this

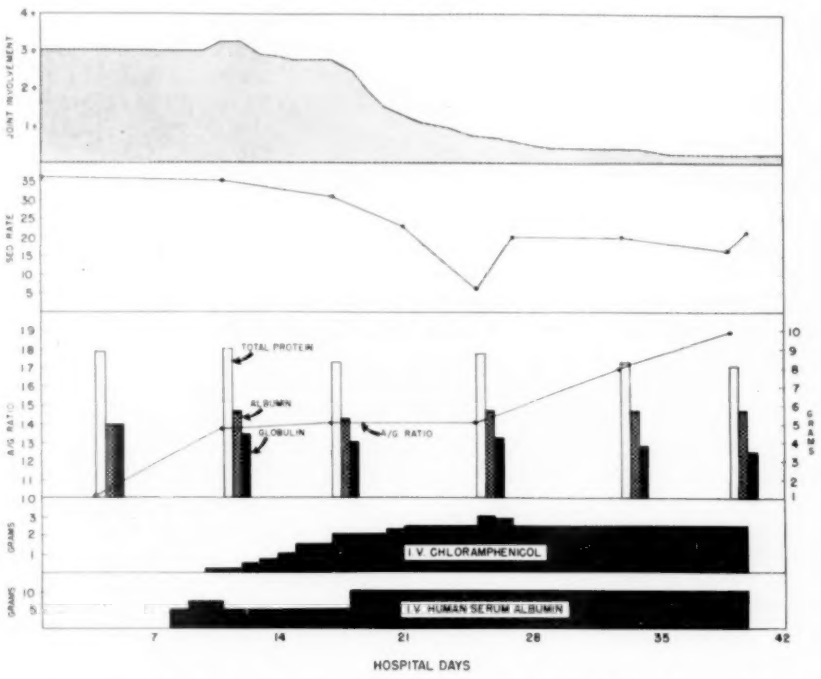

FIG. 3.—Rheumatoid arthritis, severe chronic (2 yr.) in H. T., white male, age 41. Response to treatment with chloramphenicol and albumin.

effect varied, but usually 2.5 to 10 gm. was sufficient. In some patients a mild exacerbation of symptoms was noted when more than 5 gm. of albumin was given in a single injection. Some of the latter patients showed improvement several hours later.

Five patients have been treated with combined intravenous chloramphenicol and albumin, with the object of blocking the exacerbation with albumin and allowing sufficient levels of the antibiotic to insure an adequate effect on the antigen. Fig. 3 demonstrates the response of one of these patients. There were marked clearing of symptoms and objective findings, a drop in sedimentation rate which was sustained at a lower level, an increase in A/G ratio, a rise in serum albumin, and a fall in globulin levels. It was of interest that human serum albumin appeared to influence favorably 2 cases of serum sickness, 1 severe penicillin reaction, and 1 case of acute conjunctivitis in Reiter's disease.

Summary. Evidence has been presented which supports the basic theory of hypersensitivity in the pathogenesis of rheumatic diseases. There are indications that cortisone and ACTH block the antigen–antibody reaction without affecting the basic antigen. Studies utilizing human serum albumin have been initiated in the investigation of cortisone action.

It has been suggested that the basic antigen in rheumatic diseases is a living agent, invisible in affected tissue and susceptible to the action of certain antibiotics. A parallel was found between the differential *in vitro* effect of these antibiotics on L organisms and their *in vivo* action on rheumatic subjects. The observation reported lends support to the importance of a renewed interest in the microbiological approach in rheumatic and other collagen vascular diseases. We suggest that the antigen is capable of evoking a high degree of tissue hypersensitivity. This hypersensitivity may be increased by further induced antigen release with aureomycin, chloramphenicol, and terramycin or suppressed by cortisone or human serum albumin. This new approach in the investigation of the basic mechanism in rheumatic disease must await prolonged clinical trial for final evaluation.

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PLASMA PROTEIN-BOUND IODINE DETERMINATIONS*

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In borderline cases of hypothyroidism and hyperthyroidism, the clinician is frequently put to test to establish a diagnosis. In addition to these cases, many patients with hyper- or hypometabolic manifestations present themselves for equally difficult differentiation between thyroid abnormality and other pathological situations.

Of the laboratory aids in diagnosis, only the basal metabolic rate and serum cholesterol determinations are suited for routine analysis. The validity of these 2 procedures is frequently questioned[3,4]. To obtain a truly basal metabolic rate which is regularly reproducible is difficult and demands highly skilled personnel with institutional facilities to prepare the patient. Serum cholesterol levels are influenced by a wide variety of physiological and pathological situations as well as by thyroid abnormality.

It has been well shown that plasma protein-bound iodine is representative of circulating thyroid hormone, and analysis of this compound should be a true index of thyroid function in respect to its thyroxine output[2]. The chemical determination of protein-bound iodine is technically and economically difficult when attempted by methods currently available. These techniques, in the hands of skilled personnel and special laboratories, are highly accurate and represent a real diagnostic tool. The methods, however, are not applicable to routine determinations of protein-bound iodine in clinical laboratories.

This paper describes a technique that is reproducible of a high degree of accuracy by previously unskilled technicians and seems to be suitable as a routine clinical laboratory procedure.

The technique utilizes liberated iodine as a catalyst in the oxidation–reduction reaction of a ceric–arsenite system[1,5]. The reaction is quantitative in the range of from 0.005 to 0.1 microgram of iodine.

Method. Reagents. 1) Iodine-free arsenous acid is made by dissolving 3.71 gm. of arsenic trioxide in 50 cc. of iodine-free 1-N sodium hydroxide, adding 200 cc. of redistilled water, and neutralizing with 70% (by wt.) arsenic and nitrogen-free sulfuric acid solutions. Then, 54 cc. of the 70% acid is added in excess and the volume made up to 500 cc. To this solution is added 3.125 gm. of iodine-free sodium chloride.

2) The ceric sulfate solution is made by dissolving with stirring 12 gm. of ceric ammonium sulfate in 500 cc. of 3.5-N iodine-free sulfuric acid solution.

The ceric and arsenite solutions should not react appreciably when mixed during a period of several hours.

Technique. A heparinized fasting venous blood sample is drawn in a chemically clean syringe and placed in a chemically clean test tube. All glassware must be chemically cleaned, preferably in an iodine-free solution of potassium hydroxide.

Plasma is separated from whole blood by centrifugation. Ten cubic centimeters of plasma are placed in a round-bottom test tube and the protein is precipitated accurately, according to the Somogyi method with zinc hydroxide[6]. The precipitate is washed twice with zinc hydroxide, the precipitate being separated each time by centrifugation. The protein precipitate is dissolved with 5 cc. of 2% sodium hydroxide and the test tube, stopped with cotton, is autoclaved for 30 minutes at 20 pounds' pressure at 115° C. This solu-

* This work aided in part by U.S.P.H.S. Grant H-618.

tion is filtered into a spectrophotometer tube of appropriate size, the filter paper being washed with a small amount of 2% sodium hydroxide. The filtrate is neutralized to pH 7 with sulfuric acid, and 0.4 cc. of arsenous acid reagent is added and the tube incubated at 37° C. until solution is equilibrated. The ceric ammonium sulfate solution is warmed to 37° C. and 0.5 cc. added to incubated tube which is shaken. The tube is incubated for exactly 15 minutes, and then the absorption at 480 mu is read in a spectrophotometer.

The test is standardized against various solutions of potassium iodide in ranges from 0.008 to 0.10 microgram of iodine. A blank determination is always made.

Comment. It has been possible to recover known amounts of inorganic and digested organic iodine in quantities varying from 0.005 to 0.10 microgram with an error of ±8%. This degree of error is not significant for a clinical laboratory procedure and is readily achieved by previously unskilled technicians.

A group of 60 patients has been studied using this technique. Each patient had received a diagnosis on the basis of history, physical examination, and subsequent response to treatment. Twenty-two normal persons with ages varying from 13 to 83 years had plasma protein-bound iodine levels varying from 3 to 10 micrograms per 100 cc. A group of thyrotoxic patients with ages ranging from 17 to 72 years had plasma protein-bound iodine levels varying from 12 to 46 micrograms per 100 cc. Twenty hypothyroid patients had protein-bound iodine levels from 0.2 to 3 micrograms per 100 cc.

Summary. A technique for determining circulating plasma protein-bound iodine is described. The method is reproducible of a high degree of accuracy, yet is simple enough to be used as a routine clinical laboratory procedure.

Of the patients reported here, normal persons had plasma protein-bound iodine levels varying from 3 to 10 micrograms per 100 cc., thyrotoxic patients had levels from 12 to 46 micrograms per 100 cc., while myxedematous patients had levels from 0.2 to 3 micrograms per 100 cc.

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SICKLE CELL DISEASE: STUDIES ON "IN VIVO" SICKLING AND THE EFFECT OF CERTAIN PHARMACOLOGICAL AGENTS

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Recent significant studies of the erythrocyte of sickle cell anemia reveal that an abnormal type of hemoglobin exists[10], and that the survival time of the erythrocytes of sickle cell anemia is considerably shortened[3,16]. Singer and co-workers[15] obtained survival studies of erythrocytes in this disease during an acute hemolytic crisis and a chronic stage, and could find no significant difference in longevity. If it is assumed that the basic defect of the erythrocyte is unchanged during both the acute and chronic stages of the disease, then a concept of sudden massive hemolysis of intra-erythrocytic origin as causing the acute manifestations of the disease must be questioned.

The mechanism of the crisis remains obscure. It would appear that a clinical study of a significant number of cases may be of some importance in further evaluating changes that occur in the 2 stages of the disease. In a previous review[4], emphasis was placed on evidence of organic dysfunction. Hematological studies indicated bone marrow hyperactivity and increased intravascular hemolysis that continued after disappearance of the acute symptoms. Twenty-six cases in this series were further observed. The purpose of these observations is to show the degree of *in vivo* sickling, intravascular hemolysis, and anemia during chronic and acute stages, and to observe whether significant change occurs in these phenomena to account for the acute manifestations. Certain pharmacological agents, and also blood transfusions, were given to several patients in order further to study the morbid physiology of the disease. The results obtained are presented.

Method. Eight subjects were investigated during the quiescent or chronic phase of the disease, and 10 during only the crisis or acute stage. Eight subjects were observed over a prolonged period that included both phases of the disease. Unless specified, no studies were obtained if the subject had received any therapy that might affect *in vivo* sickling. Frequent repeat-hematological studies were obtained, but only those of importance to this report are presented. In addition, some subjects in the latter group were utilized to determine the effect on sickling, hemolysis, and the resulting anemic state of: 1) blood transfusions, 2) long-term use of an anticoagulant, 3) agents to increase blood flow, 4) an oxidation–reduction agent, and 5) diet.

Stained formalin-fixed erythrocytes were obtained as described by Sherman[14]. Bizarre* and crescent forms were counted per 1000 erythrocytes and expressed in percentages. Crescent forms were characteristic of the anemic state, except in the cases to be described. The erythrocyte, reticulocyte, and serum bilirubin determinations were routinely obtained. Hemoglobin determinations correlated the erythrocyte level and are not reported. Fecal urobilinogens[12] were obtained whenever possible. The diagnostic parameter[18] served as a verification test. All were in the accepted range except during quiescent

* Bizarre forms refer to the early or incompletely sickled erythrocytes usually not having filamentous ends such as are seen in the typical crescent or completely sickled erythrocytes.

phases wherein Case 5 had a parameter reading of 20 and Case 24 had a reading of 26.

Observations. In Table 1, laboratory findings are presented. The sign—symptom complex presented by Cases 1 through 8 were easy fatigability, mild transitory pains, and occasional greenish-yellow discoloration of the sclera. None had a history within 6 months of the bone marrow, and a diagnostic parameter of over 30 were believed confirmatory. Total sickling in the group varied from slight to severe, and percentage of crescent forms apparently increased with the total degree of sickling.

Cases 9 through 18 were observed after onset of the crisis. Observations

TABLE 1.—LABORATORY DATA OF 26 CASES HAVING SICKLE CELL DISEASE DURING THE QUIESCENT AND ACTIVE PHASES

		Active Phase							Quiescent Phase					
Case	*Age*	*Time (days)*	*% Sickling*	*RBC millions/cu.mm.*	*Ret. %*	*Ser. Bil. Dir.*	*Ser. Bil. Ind.*	*Fecal Uro. mg./100 cc. (daily)*	*% "in vitro" Sickling*	*RBC millions/cu.mm.*	*Ret. %*	*Ser. Bil. Dir.*	*Ser. Bil. Ind.*	*Fecal Uro. mg./100 cc. (daily)*
1 (CH)	26								10	3.88	8.5		Tr.	
2 (EH)	15								8	2.79	9.2			117.4
		18[1]							2	4.68				967.3
3 (WW)	17								15	1.78	12.4		Tr.	722
4 (EA)	27								62	2.12	17.8		1.02	
5 (EN)	12								45	2.31	17		0.65	
6 (TR)	31								68	2.40	24		2.5	
7 (JP)	50								25	1.96	12		Tr.	
8 (FT)	27								46	2.40			2.6	
9 (TD)	16		32	3.28	4.7		1.8							
10 (CF)	27		70	2.34	18.2	2								
11 (LL)	26		14	1.70	30	4.4	Tr.	2.3						
		22[2]	46	1.9	16	2.7		3.5						
12 (JC)	20		64	1.88	16		1.2							
13 (PN)	5		42	2.45	13.9		0.91	38.7						
14 (WB)	20		49.5	2.3			3.03	322						
15 (RR)	25		54	2.6	14	6								
16 (GA)	8		44	3.4	26.8		0.3							
17 (IE)	34		20	2.80	9.9		0.37							
18 (JD)	24		36	1.84	9.3	9.3								
19 (PL)	8		52	2.15	7.7		1.7	37.6						
		28[1]							10	2.50	3.6	Tr.		
20 (BB)	8		70	2.18	14.3		2.3	54.4						
		380							60	2.12	12.2			
21 (MF)	16		49	2.7			Tr.							
		22	22	2	10.3	8								
		360							55	2.39	21		0.71	
22 (WS)	26		70	3.10										
		30							30	3.24				
23 (VJ)	17		70	2.4	18		0.5							
		90							70	2.0	10.4		1.02	
		90	20	2.59		4.18								
24 (MI)	23		57	3.63										
		780							4	3.2				
25 (JP)	24								74	3.01	18		5.8	1200
		64							60	2.84	22.3			
		341	50	3.11	13.3	6.8								
		4	60	2.93	16.6	8.4								
		72							62	2.82	17	1.8		
		182	70	2.9										
26 (JS)	24		8	2.44	16	1.2								
		60							54	2.20	29			

[1] After 1000 cc. blood

[2] Received approximately 7000 cc. blood

[3] After 100 cc. blood

the typical crisis of sickle cell anemia. Patient 3 denied ever being acutely ill. Patient 1 had no detectable crescent forms in the venous blood. The diagnosis in the latter case had previously been made. Healed ulcers of the lower extremities, habitus, hyperactivity of were made within a period of hours to days after onset, and the time of the first observation was dependent upon when the patient was admitted to the hospital. These patients usually had moderate to severe sickling, with a high percentage of crescent forms. Patient 11,

however, with severe hepatic damage, had only a few sickled forms in the venous blood when first observed. Total sickling in this subject increased during the period of hospitalization, although massive blood transfusions were given.

Opportunity was afforded to study Cases 19 through 26 during the chronic and acute stages of the disease. They presented slight to severe *in vivo* sickling, and acute episodes were not always dependent upon the degree of *in vivo* sickling. Cases 20, 21, 23, and 25 maintained severe *in vivo* sickling during both quiescent and active stages. Case 24 had a variation from 57 to 4%; Case 26 had few sickled cells when observed 6 days after onset of a crisis. Cases 21, 23, and 25 had severe hepatic damage at the time of the crisis; however, as in Case 11, *in vivo* sickling was not severe.

All subjects presented anemia during the quiescent and active stages. No significant difference could be found in the erythrocyte count of subjects showing no clinical attacks for a long period of time and those having frequent crises. This applies also to the reticulocytes. In cases in which bone marrow studies were obtained during either phase, hyperactivity was found. Case 25 had bone marrow studies immediately after onset of the crisis and 60 days later. Both showed marked hyperactivity.

Quantitative fecal urobilinogen determinations are a better index of the degree of intravascular hemolysis than the serum bilirubin. Although Case 3 revealed only negligible amounts of serum bilirubin, the daily output of fecal urobilinogen was 722 mg. In other cases in which it was possible to obtain

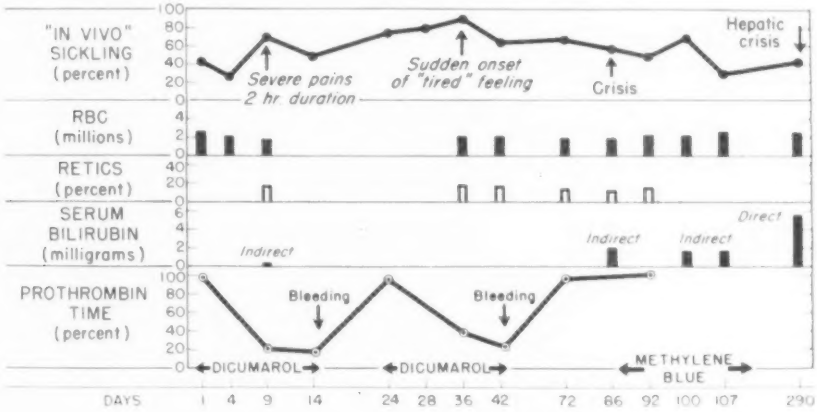

FIG. 1.—Effect of dicumarol and methylene blue (Case 23).

these studies, an increase in fecal urobilinogen output above the expected normal for age, size, and erythrocyte count was observed. Severe hepatic damage may be responsible for a decreased fecal urobilinogen output. This is observed in Case 11. The fact that massive transfusions were received may have affected this finding (*vide infra*).

In Figs. 1, 2, and 3, more detailed observations are given. Patient 23 (Fig. 1) and Patient 20 (Fig. 2) had severe *in vivo* sickling. Patient 24 (Fig. 3) usually had a mild to a slight degree of *in vivo* sickling. The time of administration of pharmacological agents to these subjects is indicated. Note that although the crisis may be associated with severe *in vivo* sickling, even more severe sickling might be present without

any clinical manifestations. Note also that at a time of casual determination during the chronic stage, the erythrocyte count was usually low and the reticulocyte count increased. No significant difference in the erythrocyte count were found. One crisis, with acute hepatic damage, was followed by a prolonged period in which the liver remained enlarged and firm. The patient was treated in another city for over a year with adequate diet, vitamins, and

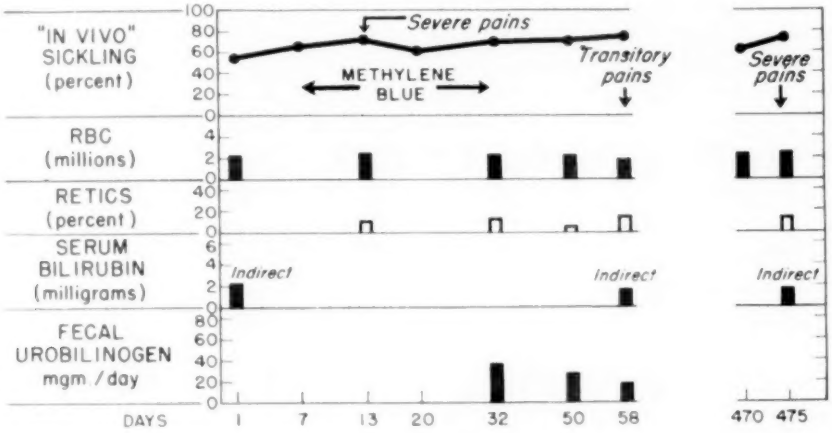

FIG. 2.—Severe *in vivo* sickling (Case 20).

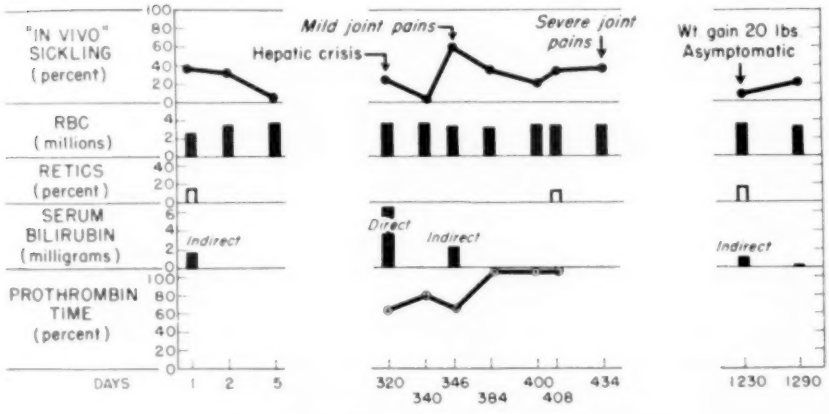

FIG. 3.—Mild *in vivo* sickling (Case 24).

during the 2 phases of the disease was observed. It must be emphasized that it was impossible to predict a crisis, and no blood counts were made immediately before the onset of a crisis. Patient 24 (Fig. 3) frequently presented only a few sickled cells in the venous blood, and at one observation no crescent cells liver extract injections. After this patient returned, a weight gain of 20 pounds was noted. There was no evidence of hepatic change, and only minimal amounts of *in vivo* sickling were present. The erythrocyte count showed no significant change.

Effects of Various Pharmacological

Agents on the Course of the Disease. 1) Blood Transfusions. Kaplan and Lewis[7] gave plasma to patients having sickle cell anemia and confirmed the phenomenon observed by Josephs[6], namely, a reduction in urobilinogen output following plasma transfusions. They also noted a reversal of this phenomenon in sickle cell anemia patients having previously had repeated transfusions. Two subjects in this series were observed following blood transfusions. Patient 2, aged 15, who had received transfusions between the ages of 7 and 10 years, was given 1000 cc. of blood. There was a marked increase in fecal urobilinogen excretion and a decrease in the percentage of *in vivo* sickling. Patient 19, aged 8 (Fig. 4), who had not previously received transfusions, likewise received 1000 cc. of blood. A decrease in the percentage of fecal urobilinogen output and in sickling was observed. The erythrocyte count rapidly returned to the previous anemia level.

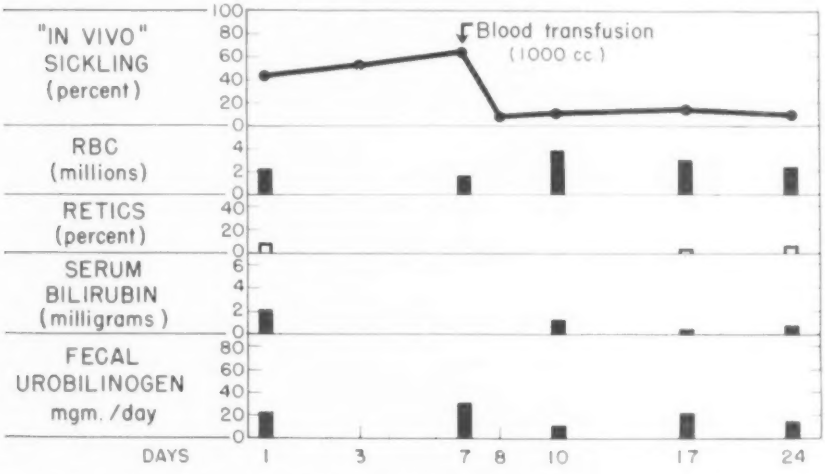

Fig. 4.—Effect of transfusion on *in vivo* sickling and on fecal urobilinogen (Case 19).

2) Anticoagulant Therapy. The rational use of anticoagulant therapy is to prevent the formation of small thrombi that are believed to occur in this disease. Murphy and Shapiro[11] used both heparin and dicumarol at the time of the crisis in their patient. There appeared to be intensification of the crisis with the use of heparin, and no effect could be noted with dicumarol. Utilization of dicumarol is to be regarded as dangerous, particularly when the predisposition to hepatic injury is considered; however, prothrombin studies in Cases 23 and 24 (Figs. 1 and 3) indicate that when evident hepatic damage was absent, the prothrombin time was within normal range. Patient 23, having no evident hepatic damage at the time, was given dicumarol in therapeutic amounts over a relatively long period during the quiescent phase. One short-lived attack of severe joint pains was experienced during this medication. Although sickling was severe, the patient usually complained only of being very tired. Repeated bleeding symptoms forced termination of the use of this drug.

3) Oxidation–Reduction Agent. Methylene blue, because of its reported effect in anoxemic states[2], was administered in Cases 20 and 23 over a period of 30 days each. One patient, Case 20

(Fig. 2), experienced a moderately severe crisis with intense sickling while on this therapy, and the drug was discontinued. The other patient, Case 23, although asymptomatic, continued to have moderately severe sickling.

4) Agents to Increase Blood Flow. Patient 11, in addition to hepatic damage, had priapism. He was given 3 cc. of tetraethyl ammonium chloride (Etamon). Objective evidence of relief was observed in a partial decrease of the priapism, and subjectively the patient felt better. Within 3 hours there was a return of signs and symptoms. Formalin-fixed blood smears revealed a slight diminution in the severity of sickling at the height of the action of the drug. Patient 24, during a period of severe joint pains, was given nicotinic acid intravenously in 100-mg. dosage. There was a transitory decrease in pains. Increasing amounts of nicotinic acid were necessary for similar effects.

5) Diet. Patients 4, 5, 6, 16, 20, 21, 25, and 26 were placed on high caloric diets over a period of 1 to 6 months. The regular feedings were fortified by a mixture containing 1 egg, equal parts of 20% cream and milk, sugar, and malt, which was given 3 or 4 times daily. Patients 16, 20, and 25 were given additional protein hydrolysates. During the period of observation, no effect could be observed on the percentage of sickling or anemia, and only slight weight changes were noted. This regimen was terminated because of the high cost and lack of evident results, although no crises were observed in any of the subjects while on this routine.

Discussion. Previous clinical observations of sickle cell anemia patients[4] reveal a protean sign–symptom complex. The presenting symptoms may be only easy fatigability and weakness for years; then frequent debilitating crises may be experienced. The manifestations may last from a few hours to weeks. It is difficult to accept a theory that a rhythmical, or periodic, increased destruction of erythrocytes can account for the disorderly symptoms of the disease. Whether intra-erythrocytic or extra-erythrocytic, other factors besides a decreased survival time and an abnormal hemoglobin must exist to explain the acute manifestations of the disease.

It appears that increased intravascular hemolysis is a more or less constant feature of sickle cell anemia. Bone marrow studies in the cases here discussed were always confirmatory of hyperactivity. No aplastic crises were noted in this series. No significant difference could be found in the reticulocyte and the erythrocyte counts of patients having frequent crises and of those who over a period of years had not had a clinical crisis. In patients observed over a long time, the erythrocyte count may be higher at the time of the crisis than during a chronic phase of the disease. Variations in sickling may be noted. Subjects may reveal severe *in vivo* sickling during both phases of the disease, while others may have only mild to slight sickling. Although the crisis was frequently noted at a time of severe *in vivo* sickling, it is noteworthy that even more severe *in vivo* sickling could occur without the acute manifestations. Likewise, the crisis may be experienced with only a few sickled cells in the venous blood.

Fecal urobilinogen determinations usually indicated increased intravascular hemolysis even when the serum bilirubin was low. However, even this determination is dependent upon the state of liver function or dysfunction, as seen in Case 2. Lowe and Adams[8] recently published detailed studies of hepatic episodes and pointed out that there may be variations in urobilinogen

output during the course of the disease. A liver biopsy obtained on 1 subject in the series (Case 23), during a severe hepatic episode, revealed a large collection of pigment in the liver cord cells and within the large Kupffer's cells, with a collection of large and small mononuclear cells not limited to any particular area.

The effects on urobilinogen excretion of blood transfusions have been noted, and the studies are comparable with those of Kaplan and Lewis[7]. The marked decrease in sickling in 2 cases suggests some effect on the degree of *in vivo* sickling that is not dependent upon the number of normal erythrocytes transfused. A rapid return to the pre-anemic level, without significant change in degree of *in vivo* sickling, was noted in Case 19. The use of an anticoagulant (dicumarol) did not prevent a severe, but short-lived, acute episode, although the prothrombin time was significantly increased. Whether a prolonged crisis was prevented is not known; however, severe intravascular hemolysis and anemia continued while this agent was being given. An oxidation–reduction agent (methylene blue) had no effect on the course of the disease. Although the rate of blood flow is increased in sickle cell anemia, it appears that a further vasodilating action of administered therapeutic agents resulted in temporary relief. No clinical attack was experienced by subjects on adequate diet; however, no significant change was noted in the degree of *in vivo* sickling or the erythrocyte count.

Cases 1 (previous history) and 24 presented the typical manifestations of the acute episodes of sickle cell anemia, and only a relatively few sickled cells at the time of the examination. At the height of *in vivo* sickling, only a few crescent forms were noted in the venous blood in Case 24, and formalin fixed specimens were more suggestive of the trait than of active sickle cell anemia. Both of these subjects maintained a higher erythrocyte count than the others. Electrophoretic determinations[10], electron microscopy examinations[11], and longevity studies[3,15] on erythrocytes of similar subjects may reveal that a transition phase exists between the trait and active disease. Recent studies by Neel[9] and Itano and Neel[5] do indicate that a much milder type of sickle cell anemia exists which has a different genetic basis, and presents another abnormal type of hemoglobin.

The severity of intravascular hemolysis does not adequately explain the acute manifestations of the disease. Case 25, with a high indirect serum bilirubin and fecal urobilinogen output, had no significant crisis until nearly a year later. Other subjects had no crisis for years, although severe intravascular hemolysis was present. Previous reports on bizarre findings in subjects with the sickle cell trait[1,17,18] suggest that an occlusive phenomenon may occur without evidence of increased intravascular hemolysis or severe *in vivo* sickling. The protean manifestations of sickle cell disease, with isolated regions primarily affected, further suggest that the rate of blood flow to the organ plays an important part in the sign–symptom complex.

Summary and Conclusions. Twenty-six subjects having sickle cell anemia were observed during the acute and chronic phases of the disease. Increased intravascular hemolysis is a more or less constant feature of the disease, and the resulting anemia and accelerated erythrocytogenesis are found during both periods. Sudden massive destruction of the erythrocytes does not appear to explain the symptoms at the time of the crisis.

Variations of *in vivo* sickling may occur. The clinical crisis may be associated with few or numerous sickled forms in venous blood. Although severe

sickling was often associated with the crisis, even more severe sickling may be observed without clinical symptoms.

The effects of certain pharmacological agents on the course of the disease are presented, and the results are as follows: 1). An anticoagulant agent (dicumarol) did not prevent a transitory attack of pain.

2). Increase in the blood flow appeared to give transitory relief during a crisis.

3). An oxidation agent (methylene blue) had no effect on the course of the disease.

4). An adequate diet did not appear to affect intravascular hemolysis.

5). The results of blood transfusions are in agreement with the findings of Kaplan and Lewis[7].

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AN APPRAISAL OF TRANSORBITAL LEUKOTOMY

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THE procedure of transorbital leukotomy, although introduced by Fiamberti[5] in 1937, has had a relatively short history due to the intrusion of World War II. However, following the war, Fiamberti[6] once again renewed interest in this method, and Freeman[7] transplanted the technique to the United States in 1946, since which time he has operated upon over 400 patients[8] and modified the method[9].

During the early development of the classical form of prefrontal lobotomy, results varied somewhat in different clinics due to variations and modifications of the original technique. Moreover, there were considerable discrepancies between the intended plane of sectioned frontal lobe and the actual findings on autopsy material, as was so clearly demonstrated by Meyer, Beck and McLardy[22]. Despite this, the gratifying results reported by the Board of Control[1], the Connecticut Cooperative Lobotomy Study[16], and individual observers, justified the use of this admittedly still crude method. Transorbital leukotomy is now emerging from a similar phase of development, and the discordant notes here and there may be attributed to differing techniques, limited experience, the quality of case material, and the manner of appraising results.

Fiamberti[5] originally severed the frontal subcortical white matter and in some cases injected either absolute alcohol or 10% formalin. Fernández-Morán[3] operated upon 21 patients 25 times and observed that in reoperated cases the additional injection of novocaine into the white matter produced better results than section alone. By and large, the majority of cases operated upon thus far have been by section of frontal subcortical white matter, using a pointed leukotome. The goal to be achieved is severance of a sufficient quantity of thalamocortical fibers to the frontal pole to produce the maximal desired effect without the introduction of undesirable personality alterations. The techniques employed have been described by Fiamberti[5], Freeman[7-9], and Moore[23].

Ferrero[4], Walsh[28], and Rizzatti and Borgarello[21] had little to say in favor of the operation of transorbital leukotomy. The results reported by Fiamberti[5], and Fernández-Morán[3] were encouraging but not openly optimistic.

Freeman, in a series of articles[7-13], has taken an increasingly affirmative stand regarding the validity and effectiveness of the procedure, and indeed feels that in many respects it should supplant the method of prefrontal lobotomy[14]. Jones and Shanklin[18] operated upon 41 state hospital patients without fatality and reported improvement in 80% and parole of 53%. A more recent report by these authors[19] claimed recovery in 28 of 74 patients upon whom they operated. There were no fatalities and no complications in their series. Good results were obtained by Haas and Williams[17] in a small series. Rusk[12] performed transorbital

[*] Presented before the International Congress of Psychiatry, Paris, September 18-27, 1950.

leukotomy upon 400 patients, most of whom were chronically disturbed; the result was a 20% discharge from hospital. Tait[37] stated that approximately one-third of 59 state hospital patients who had transorbital leukotomy performed were discharged and have maintained improvement.

Personal experience with 212 cases permits of a closer analysis and appraisal of the indications for, and results and complications of, transorbital leukotomy. One series of 110 private patients was studied and reported in collaboration with Winkelman[26], and another series of 102 state hospital patients was studied and reported in collaboration with Hill and Lutz[25].

Clinical Material. The private group of 110 patients consisted of 78 females and 32 males, the ages ranging from 14 to 70 years. In this group 127 transorbital leukotomies were performed. Difficult cases, resistive to the various accepted forms of present-day treatment, were selected at random in order to test the validity of the operation. There were 74 cases of schizophrenia, consisting of paranoid, catatonic, deteriorating, and pseudoneurotic types; 14 cases of the affective disorders; 19 cases of psychoneuroses, mainly obsessive–compulsive and anxiety–tension–phobic states; 2 cases of paranoid psychosis; and 1 case of mental deficiency with paranoia. The operative techniques employed in this series consisted of the original Freeman method[7], his modified "deep frontal cut"[9], and the modification of Moore[23]. These patients have been observed for from 3 months to 2 years postoperatively.

The state hospital series of 102 patients was comprised of 60 females and 42 males, the youngest being 18 and the oldest 54 years of age. These patients had previously been treated at private and state institutions with the present forms of psychotherapy and shock modalities. The duration of illness ranged from 2 to 24 years. The diagnostic categories were schizophrenia (hebephrenic, catatonic, paranoid, and mixed types), 97 cases; involutional melancholia, 2 cases; mental deficiency with psychosis, 2 cases; psychopathic personality, 1 case. The majority of these patients were "back" ward cases considered permanently non-salvageable. The operative techniques used were the original Freeman method[7] and the Moore modification[23]. There were no re-operations. The period of post-operative observation in this group has been from 2 to 10 months.

There were 2 patients in each of the 2 series upon whom unsuccessful prefrontal lobotomies previously had been performed, and 1 patient had been subjected to thalamotomy on 2 occasions without success. The pre-operative and post-operative care in both series was that outlined in an earlier communication[23]. The instrument employed throughout was a transorbitome[24].

A total of 26 patients in both series was selected at random and subjected to a battery of psychological studies before and after operation.

Results. Despite the dissimilarity of the case material in these 2 groups, there was a striking parallel of response to transorbital leukotomy in the schizophrenic and affective-disorders groups. Among the 110 private patients, 35.5% were capable of returning to their homes and effecting a satisfactory socio-economic adjustment equivalent to total recovery. Of the 102 chronically-ill state-hospital patients (Chart 1), 28 were discharged from the hospital to resume their former occupations or housework.

In the first group of 110 the total over-all improvement rate in the various categories was as follows: Schizophrenia, 53% (paranoid 63%, catatonic 74%, hebephrenic and simple 17%, pseudoneurotic 100%); manic depressive psychosis, 83%; involutional depression, 63%; psychoneuroses, 84%; paranoid psychosis, 50%; mental deficiency with paranoia, 100%. The improvement rate of the total series was 61%.

The over-all improvement rate in the state-hospital group, using a weighted Malamud rating scale[21], is as follows, and may be compared with the above figures: Schizophrenia, 75.2% (paranoid 84.6%, catatonic 88.2%, hebephrenic 61.5%, mixed types 72.6%); involutional depression, 100%; mental deficiency with psychosis, 50%; psychopathic personality, 100%. The improve-

ment rate of the total series was 75.5%.

Comparison of the two groups of figures shows that among the schizophrenic subdivisions, the catatonic patients reacted most favorably, with the paranoid next in order, and the hebephrenic or deteriorating types least responsive. This should not, however, be applied as a hard and fast criterion for selection of cases, as will be discussed later. The 2 cases of involutional depression in the state-hospital series made a complete recovery, and among the 14 patients with affective disorders in the first series, 72% improved.

Only 3 of the 19 psychoneurotics failed to respond to transorbital leukotomy. Two of these were patients with a long history of pronounced hypochondriacal preoccupations. The case of psychopathic personality was of 11 years' duration and the response was dramatically gratifying.

One of the 4 patients previously subjected to lobotomy by the prefrontal technique, with unsuccessful results, improved following transorbital leukotomy. Another improved temporarily, after transorbital leukotomy, then relapsed and has been maintained at a moderately improved level by means of electric convulsive therapy. One severe obsessive–compulsive patient had been subjected to thalamotomy twice unsuccessfully, but following transorbital leukotomy has made remarkable improvement, with socioeconomic recovery.

In both series, but notably in the state-hospital group, it was found that, contrary to expectations, patients ill as long as 14 years made total recoveries, and that improvement was almost equally distributed throughout the spectrum of duration of illness extending across 24 years. This can be seen from the results in the 102 state-hospital cases.

The observation that the patients with affective disorders who improved after transorbital leukotomy were those who had previously responded favorably to electric convulsive treatment, albeit they relapsed, was common to both series. It was also noted in both groups, that among the patients who were not benefited by transorbital leukotomy alone, a number showed improvement with a post-operative series of electric convulsive therapy, whereas prior to transorbital leukotomy they responded poorly to electric convulsive treatment.

More than one-third of the 17 patients subjected to re-operation in the first series of 110 cases improved. Re-operation was performed because of relapse or failure to obtain maximal improvement. In all, a more extensive sectioning was carried out on the second venture.

In both groups it was observed that among the schizophrenic patients who failed to respond satisfactorily immediately or shortly after operation, a small percentage developed abrupt improvement in from 2 to 6 months post-operatively.

The 26 patients who received psychological studies (which included the Wechsler-Bellvue Intelligence Scale, Form I; Shipley Institute of Living Scale; House-Tree-Person Drawings; Machover Body Form; Bender-Gestalt, Rorschach, and Szondi tests) revealed no evidence of intellectual deficits and no introduction of abnormal personality patterns. None of the 208 surviving patients was made worse by the procedure.

Analysis of the clinical aspects of the recovered and improved patients disclosed that transorbital leukotomy appeared to establish its salutary effects by the following: 1) removal or lessening of anxiety; 2) marked diminution of complaint inventory; 3) abolition or reduction of agitation, excitement, aggression, overt hostility and

destructiveness; 4) elimination or lessening of overt hallucinatory episodes and diminution of subjective response to disclosed hallucinatory content; and 5) extinction or lowering of autonomic abnormalities such as vasomotor instability, frequency of urination, tachycardia, and evidence of hypermotility of the gastrointestinal tract. Paralleling this, the significant changes among the improved patients as revealed by the battery of psychological studies were: decreased anxiety and preoccupation with self, better control of explosive affective responses, less rigidity of personality, better organization of thinking, and improved judgment.

The collective experience from these two series of patients suggests that the length of illness and the diagnostic category should not be the determining factors in the selection of cases suitable for transorbital leukotomy, or other types of psychosurgery, but that the presence of the following semeiotic features may constitute more reliable criteria for achieving the best results from operation: 1) anxiety, tension; 2) inventory of complaints, preoccupation with self; 3) agitation, aggression, destructiveness; 4) labile affective tone; 5) autonomic abnormalities; and 6) previous favorable temporary response to courses of electric convulsive therapy.

In addition to adherence to these criteria, patients selected for operation should be only those who have failed

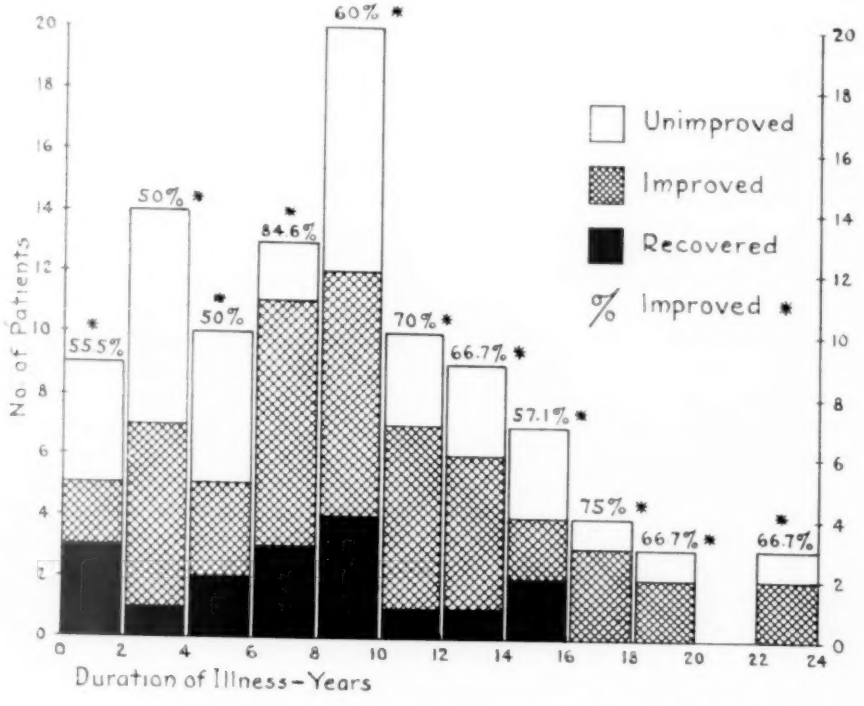

CHART 1.—Results in 102 post-leukotomy patients, Wernersville State Hospital, Pennsylvania, as of September, 1950. This graph portrays the distribution of over-all improvement rates throughout the "duration of illness" spectrum: 17 complete recoveries extend from 2 years to 16 years' duration of illness. There is improvement present in every duration-illness group up to 24 years. Not shown here are 28 discharged patients now at home.

to respond to the accepted methods of psychiatric treatment now employed.

We have had no experience with transorbital leukotomy in pain cases. However, Freeman[8,12] has reported favorable results in severe chronic pain of terminal carcinoma.

Complications. Among the 212 patients on whom 229 transorbital leukotomies were performed, there were 5 post-operative hemorrhages. One patient completely recovered following removal of an intracerebral clot and 4 succumbed. One of these patients was a hemophiliac, which information was withheld by the parents until after operation. Another had had a frontal lobe softening antedating operation, and the intracerebral hemorrhage found at autopsy was confined to the area of softening in one frontal lobe. The combined mortality rate was 1.9%.

In the 350 cases reported by Freeman[9], there were 2 fatal hemorrhages and 2 deaths from other causes, a mortality rate of 1.1%. There were 3 deaths, or 0.75% mortality, among 400 patients reported by Rusk[12]. Fernández-Morán[3] reported no post-operative complications or deaths in 21 patients after transorbital leukotomy. Haas and Williams[17] performed the operation on 24 patients without a fatality. Jones and Shanklin[19] have recently reported 74 cases of their own, without a fatality or post-operative complication.

These statistics may be compared with the mortality rates of other types of psychosurgery: 3% mortality in 1000 cases of prefrontal lobotomy reported by the Board of Control, England and Wales[1]; 2.4% in 700 cases of frontal lobotomy reported by the Connecticut Cooperative Lobotomy Study[16]; 6% in 48 prefrontal lobectomies by Peyton, Noran and Miller[28]; 3.2% in 44 thalamotomies by Spiegel and Wycis[35]; 3.7% in 107 cases of frontal lobotomy (Lyerly technique) by Oltman *et al.*[27]; and 4.6% in 43 cases of selective cortical undercutting by Scovill[33], a mortality rate which has been reduced in his most recent series[34] of 124 patients to 1.6%. Pool[29] stated that there were no operative fatalities in 52 cases of topectomy which he reported and none in 125 topectomies now done.

Urinary incontinence occurred in 21 of the 212 patients. It terminated without treatment in 24 to 72 hours in all but 2 patients, in whom it persisted for 17 and 30 days, respectively. Drowsiness appeared in 5 patients, lasting 1 day in 4, and 1 week in 1 patient. Low-grade fever was present in 2 patients for 1 week. One patient had a periocular hematoma which subsided within 72 hours and completely resolved in 5 days. Cerebrospinal fluid leak into the conjunctiva occurred in 1 patient, but this cleared up spontaneously on the third post-operative day. Meningismus was present in 1 patient for 1 week. A patient who had had approximately 100 electric convulsive treatments prior to operation developed a few convulsive seizures after transorbital leukotomy, but these disappeared spontaneously after a second transorbital leukotomy, which effected an excellent psychiatric recovery. To date, no post-operative epilepsy has appeared in the 212 cases. There were no post-operative infections in either group of cases. These relatively mild, innocuous complications are met with in other series of transorbital leukotomy, and the absence of post-operative epilepsy and infection is common to the various series reported thus far.

Post-operative complications in other forms of psychosurgery are often of greater moment than those just cited for transorbital leukotomy. Post-operative convulsive seizures in uncomplicated prefrontal lobotomy occur in 7% of the cases[13], whereas re-operation or lobotomy done on patients who previously received numerous electric con-

vulsive treatments results in a 20% incidence of epilepsy[13]. Scoville[34] reported isolated early seizures in 10% of his patients with selective cortical undercutting. Among topectomized patients 14% have had 2 or more seizures post-operatively[20]. The incidence of post-operative epilepsy in lobectomy is 28%[28]. Among 41 patients after thalamotomy, 1 (2.4%) developed convulsive seizures[35].

Other complications attending prefrontal lobotomy, selective cortical undercutting, lobectomy, topectomy, and thalamotomy include: urinary incontinence lasting longer than 1 month in 17.3% of lobotomies[16]; incontinence of bowel[15]; edema and trophic disturbance of the lower limbs[39]; somnolence, psychomotor retardation; neurological signs (ptosis of eyelid, impairment of extra-ocular movements, motor weakness in a limb), sensory disturbance, memory defects[35].

Discussion. The ultimate fate of the individual forms of psychosurgery and the broad concept of psychosurgery itself will be determined dually by its scope of safe, effective usefulness as arrived at by such carefully controlled studies as the Board of Control (England and Wales)[1], the Connecticut Cooperative Lobotomy Study[16], the Columbia–Greystone Associates[2], and the advent of superior nondestructive procedures or biochemical measures.

Psychosurgery thus far has proved to be a valuable, though not fully satisfactory, aid for those hosts of psychiatric patients who had been finally rejected as incurable because of their failure to respond to repeated courses of psychotherapy, shock modalities, and time itself. The practical problem posed in the use of psychosurgery as a part of a state-hospital program or by the advising physician is its effectiveness, safety, availability, and cost.

Although "comparisons do ofttime great grievance"[20], the peculiar needs, indications, and shortcomings to be found in each type of psychosurgical procedure require that we place each on the balance and note its comparative weight. The following dictum of Freeman[12] applies cogently to transorbital leukotomy: "From the clinical standpoint, the operation of leukotomy should be adapted to the needs of the patient. An inadequate operation is useless; a too extensive operation is crippling. Granted that the patient has not deteriorated beyond recall, in which case no operation should be performed, the leukotomy should be just sufficient to relieve the neurotic or psychotic preoccupation with the self, without at the same time trespassing upon those parts of the frontal lobe that are necessary for adequate social reintegration". Moreover, there are certain considerations which prefrontal lobotomy, topectomy, cortical undercutting, thalamotomy, and lobectomy do not fully meet. These methods require moderate or extensive surgical attack; they are time consuming, and in the case of thalamotomy, elaborate preparation is necessary; the services of a neurosurgeon, of whom the number is limited, is required; the duration of hospitalization is that of a craniotomy or longer in the case of prefrontal lobotomy; nursing care may be extensive; and expense to the patient or institution is relatively high.

Transorbital leukotomy, on the other hand, offers the advantages of: 1) ease of performance: it can be done by a competently trained psychiatrist or neurologist in the various mental institutions using this technique; 2) economy of time: 12 to 15 patients can be treated by this method in the same time required for 1 patient with most of the operative methods named above; 3) minimal hospitalization and nursing care: patients can be discharged from the hospital in 2 to 4 days; 4) minimal expense to patient and institution; and

5) the clinically important feature that it does not impair the intellectual endowments of the patient or introduce undesirable personality traits, which so commonly follow prefrontal lobotomy[30,32,36].

In view of these favorable aspects, transorbital leukotomy lends itself well for institutional use. Also because of these reasons, permission for re-operation is readily secured. Furthermore, if re-operation fails of its goal, the more extensive types of psychosurgery may still be resorted to. In this regard Freeman's statement[12], "Of 15 patients having first the transorbital operation then followed by major leukotomy, only 3 derived further benefit", is of interest. One of our cases showed striking improvement for 3 months following transorbital leukotomy, but relapsed, and topectomy was then performed but without gain. Conversely, 2 patients previously subjected to lobotomy and one unsuccessfully to thalamotomy improved following re-operation by the transorbital approach. These latter observations, plus the favorable clinical results obtained with transorbital leukotomy, give it, with respect to the range of effectiveness, a rank comparable with the major psychosurgical procedures. The other factors of simplicity, ease of performance, availability, safety, and economy should recommend this method to those innumerable patients who have been lost to society.

Summary. The historical development of transorbital leukotomy, a form of frontal lobotomy originated by Fiamberti, is traced, and the results obtained by this procedure as reported in the literature are given.

The personal experience of the author with 212 cases of a variety of psychoses and psychoneuroses operated upon by this method is described and the comparative results in the different diagnostic categories are discussed.

The criteria essential for optimal results in transorbital leukotomy are embodied in the presence of a group of certain symptomatic features outlined in the text.

The complications and mortality statistics of transorbital leukotomy are compared with those of other forms of psychosurgery, and the advantages of transorbital leukotomy are stated.

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THE MUSICAL MURMUR OF AORTIC INSUFFICIENCY: CLINICAL MANIFESTATIONS; BASED ON A STUDY OF 18 CASES*

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Musical diastolic murmurs of aortic insufficiency are relatively infrequent. They are usually characterized by a striking musical quality and are frequently so loud that they can be heard over the entire precordium; at times they are audible to the patient. The following terms have been used in describing the murmur: "cooing of a dove," "buzzing of a saw," "like a cuckoo clock," "like the spinning of a top".

Although originally described by Hodgkin[15] in 1829, the significance of these musical murmurs has remained obscure until relatively recently. The work of Scott[23] and others[13,25,27,28] has served to emphasize the role of syphilis and retroversion of an aortic valve in their causation. In addition, these murmurs have been attributed to the following conditions: mitral lesions[10], irregular calcification of the aortic orifice[24], anomalous cord between the ventricular wall and septum which is put on tension during ventricular filling[30], cribriform aortic valves[3], and other cardiac abnormalities.

In the more recent literature, the musical diastolic aortic murmur has been reported chiefly in 3 conditions: 1) retroversion of an aortic leaflet[4,15,23,25,27,28], which is usually associated with syphilitic aortic insufficiency but occasionally occurs in rheumatic disease[4,25] with aortic insufficiency; 2) rupture of an aortic cusp[5,8,14,16,17,18,19,22,29] occurring spontaneously or following trauma; and 3) bacterial endocarditis[7,8,9,14,22].

In 1939 we became interested in patients presenting this murmur, and at that time we reported a series of 11 cases[4]. Since then we have studied 18 additional cases which form the basis of this report. Recent experience has altered in 2 respects our original ideas as to etiology on this subject. We have seen additional cases of rupture of the aortic valves, and, because of the newer chemotherapeutic measures, we have followed additional cases of bacterial endocarditis from the acute into the healed stage. Our views concerning the serious prognosis presented by patients with retroversion of the aortic leaflets have also undergone revision.

Material. The etiology of these 18 cases was as follows: syphilis, 11; rupture of an aortic cusp, 2; acute rheumatic fever, 2; bacterial endocarditis, 3 (1 acute and 2 subacute). These patients were studied clinically, and 1 or more heart sound records were obtained in each subject. Necropsies were obtained in 5 of these patients (2 with ruptured leaflets, 2 with eversion in association with syphilitic aortic insufficiency, and 1 with rheumatic heart disease).

Clinical Manifestations. These patients presented certain cardiac findings in common. The most outstanding

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of these was the presence of the musical diastolic murmur, accompanied by a diastolic thrill, at the base of the heart. Although the murmur was usually most intense at the base, it could be heard over the entire precordium and was transmitted to the chest wall posteriorly and frequently to the shoulders, elbows, and the cranium. Four of these patients complained of a disturbing noise in their chests which interfered with their sleep and intensified their anxiety. In case 7 the murmur was distinctly audible to the wife of the patient at a distance of several feet. The murmur varied in intensity and musical quality in different patients and in the same patient on different days. The heart was always enlarged, and the classical signs of aortic insufficiency were present. The severity of the cardiac disturbance, clinical manifestations, and course varied with the underlying etiology.

The group with syphilitic aortic insufficiency comprised the largest of the series (11 cases). The time of the murmur's appearance was clearly defined in 6 patients; it followed severe exertion and was accompanied by a moderate grade of shock and precordial pain. The syphilitic patients, although apparently able in most instances to make a satisfactory adjustment to the altered circulatory dynamics, were subject to episodes of severe substernal pain, paroxysmal dyspnea, and congestive heart failure. In the patients with syphilitic aortic insufficiency the musical quality persisted with only slight modification. This was substantiated by a relatively long period of observation of 4 cases. Two patients were kept under observation for a period of 1½ years and two for 5 and 6 years, respectively. Nine of the 11 syphilitic patients had positive serologic reactions; one with a negative Wassermann test showed at necropsy unmistakable evidence of syphilitic aortitis and valvulitis; another, also with a negative Wassermann test, gave a history of a penile lesion and had received extensive anti-syphilitic treatment.

In our previous experience (1939)[4], 9 of the 10 patients with syphilitic aortic insufficiency died while under observation. The patient who lived was observed for a period of 3 years. In those that died, the longest interval between recognition of the murmur and death was 10½ months, and the shortest interval 3 weeks; the average was 14 weeks. In the present series 3 patients died 4½ months, 18 months, and 7 weeks, respectively, after recognition of the murmur. Of the living patients, 1 has been observed for a period of 6 years, 1 for a period of 5 years, and 2 for 18 months. The remaining 4 cases could not be followed for various reasons. Our recent experience suggests that the prognosis of this condition is not so grave as it was formerly thought to be.

In our experience the appearance of a musical diastolic murmur in bacterial endocarditis is relatively rare. The murmur appeared on the 26th day of the illness in the patient with acute bacterial endocarditis, and the musical quality of the aortic diastolic murmur persisted for 2 years; it was then replaced by a blowing diastolic murmur. In 1 patient with subacute bacterial endocarditis, the musical murmur was present on admission and this quality persisted after 17 months. In the other patient the musical murmur which was audible on admission persisted until death, 20 days later.

In the 2 cases of rheumatic heart disease, the musical murmur appeared during an attack of acute carditis. In one of these the musical murmur appeared on the day after admission and persisted without modification until death 10 weeks later. In the other the

musical murmur was present for 10 days; a blowing diastolic murmur then replaced it.

The cases of rupture of the aortic valve occurred in patients with advanced grades of hypertensive cardiovascular disease. The onset in both of these patients was sudden and was ushered in by an attack of severe precordial pain accompanied by a state of shock. One patient succumbed in 4 days; the other died 4 weeks after rupture of the aortic leaflet.

Brief reports of the necropsied cases and of one case of acute bacterial endocarditis follow.

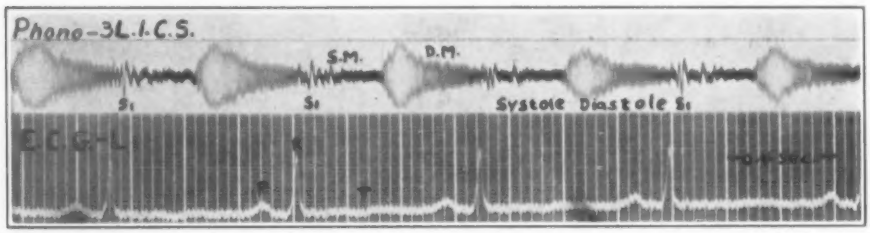

FIG. 1.—(Syphilitic aortic insufficiency.) The musical murmur starts immediately after the second heart sound, is rapidly crescendo with a gradual decrescendo, and occupies the entire diastole. Initially there are 340 vibrations per second and terminally 210 vibrations per second.*

Case Reports. CASE NO. 1. R. H., a 39-year-old colored man, was admitted to the hospital 3 times between Sept. 2, 1939, and Dec. 13, 1939. About one year prior to the first admission, he developed precordial and substernal pain at rest and following exertion, dyspnea on effort, and ankle edema. These symptoms increased up to the time of his first admission. The heart was enlarged to the anterior axillary line in the 6th intercostal space. Quite striking was a marked diastolic thrill and a loud, high-pitched, musical diastolic murmur, loudest in the 3rd left interspace at the border of the sternum (Fig. 1). The typical peripheral signs of aortic insufficiency were present. The blood pressure was 160/44. Crackling rales were present over both lung bases, the liver was palpable and tender, and there was marked swelling of the ankles. The electrocardiogram showed inversion of the T wave in lead I and the left precordial leads. The Wassermann test was negative, but there was a history of a syphilitic infection with anti-syphilitic treatment. After 3 weeks' treatment for the congestive failure, he was discharged improved. One month later he was readmitted with the above findings, plus those of a right-sided hemiplegia, which gradually cleared after 4 weeks. His 3rd and final admission was on Dec. 13, 1939, at which time he complained of substernal pain, paroxysmal nocturnal dyspnea, and ankle edema. Evidence of a severe grade of heart failure was present during this admission. Despite treatment, his course was downhill and he died on Jan. 17, 1940.

At *necropsy* the aorta showed adventitial fibrosis and mononuclear cell infiltration with other evidence of marked syphilitic aortitis. The right anterior cusp of the aortic valve was everted, and the free edge was flaplike (Fig. 2). Syphilitic pachymeningitis was the cause of the hemiplegia.

COMMENT. This represents a typical case of syphilitic aortitis with eversion of the right anterior aortic cusp. The heart-sound record of the diastolic murmur in this patient showed the highest-pitched murmur in this series; its vibration frequency ranged from 340 to 210 vibrations per second (Fig. 1).

CASE NO. 2. O. D., a colored man 45 years of age, was first admitted to the medical ward of the Philadelphia General Hospital Dec. 14, 1944. For one year prior to admission he complained of dyspnea on exertion and of having to sleep in a semi-reclining position. Physical examination revealed the heart to be enlarged to the anterior axillary line in the 6th intercostal space. There was a marked

* *Symbols:* S1, first heart sound; S.M., systolic murmur; D.M., diastolic murmur.

thrill and a Grade 5 musical, high-pitched diastolic murmur was heard over the entire chest; it was loudest over the sternum at the level of the 3rd intercostal space. Classical peripheral signs of aortic insufficiency were present. The blood pressure was 170/50. The electrocardiogram showed flattened T waves. The Wassermann test was positive. With digitalization and bed rest, the patient improved greatly in a period of 3 weeks and he was discharged to the Heart Clinic. On the next hospital admission 1 year later, he again showed signs of congestive failure. The physical signs were unchanged from those noted above. He was readmitted for the 3rd time on May 9, 1946, because of fever, pains in his chest, and a productive cough. Examination showed the lungs to be clear to percussion, but crackling rales were heard over both lung bases posteriorly. Examination revealed no significant change in the cardiac findings. Two days after admission the temperature became spiking in character, and there were signs of consolidation in the lower lobe of the left lung. The blood culture was positive for Pneumococcus Type XIX and penicillin was started. The patient died on the 7th day after admission.

Necropsy Findings. The heart weighed 740 gm. The aorta showed signs of syphilitic aortitis with minimal atherosclerosis. The heart showed fibrinous pericarditis, syphilitic aortic valvulitis, bacterial endocarditis of the aortic and mitral valves, biventricular dilatation and hypertrophy, and acute myocarditis. The aortic valve ring was stretched, the right anterior cusp was everted, and all 3 cusps were covered with friable yellowish red vegetations. There were 2 large vegetations on the mitral valve.

COMMENT. This case presents the typical findings of syphilitic aortitis and aortic insufficiency with eversion of the right aortic cusp. Bacterial endocarditis, caused by Pneumococcus Type XIX, was superimposed on the syphilitic valvular lesions.

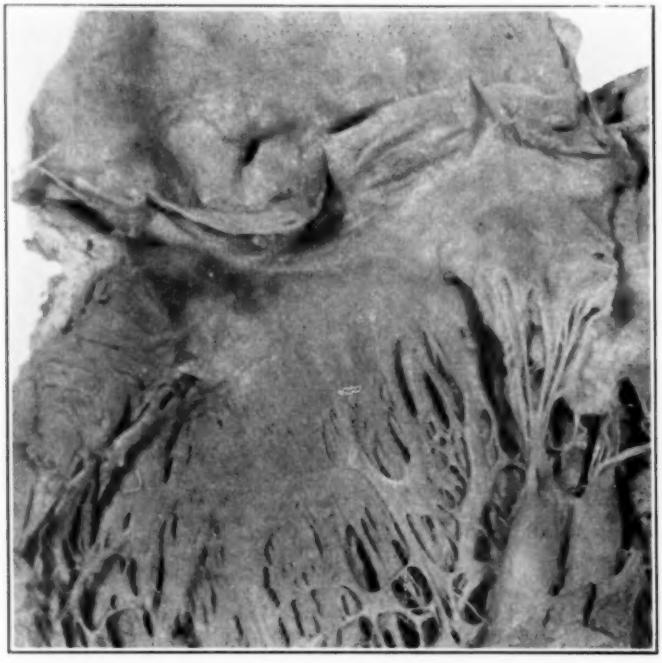

FIG. 2.—Note a patch of syphilitic aortitis surrounding and narrowing the orifice of the right coronary artery. Below this is the everted right anterior aortic cusp.

CASE No. 3. F. K., a 54-year old colored man, had been an attendant at this hospital and a patient of the Heart Clinic for 4 years, the diagnosis being hypertensive cardiovascular disease with episodes of heart failure. His blood pressure ranged from 160 to 180

systolic and 110 to 140 diastolic. On May 5, 1948, he was admitted to a medical ward; he had suddenly developed marked shortness of breath and severe substernal pain which radiated to both shoulders. The patient was markedly dyspneic and in a moderate state of shock. The previously clear, accentuated, aortic second sound was replaced by a loud, high-pitched, musical diastolic murmur, audible over the entire precordium. A marked diastolic thrill accompanied the murmur. The blood pressure had dropped to 110/50. The heart was enlarged to the 6th left intercostal space in the anterior axillary line. The lungs were clear. The substernal pain continued but was relieved somewhat by opiates. The electrocardiogram showed marked T wave inversion in all leads. Despite supportive measures, the patient failed rapidly and died 2 days after admission.

Necropsy. The heart weighed 530 gm. There was evidence of left ventricular hypertrophy. The chief point of interest was confined to the aortic valves. The right anterior cusp sagged downward toward the left ventricle because of ulceration and loosening of its commissure adjacent to the non-coronary cusp. Centrally this cusp presented 2 rounded aneurysms with soft, friable walls (Fig. 3); the intact one measured 0.8 cm. in diameter; the second had completely ruptured, producing a perforation of the leaflet about 0.8 cm. in diameter with turned-out, ragged, friable edges.

COMMENT. In this case with hypertensive arteriosclerotic heart disease, the musical murmur was produced by rupture of a degenerated valve cusp. It is interesting to note that the right anterior cusp was the leaflet involved.

CASE NO. 4. R. P., a 43-year old colored man, was apparently in good health until Jan. 14, 1948, when he developed a sudden attack of shortness of breath and cough, following which he was admitted to the hospital. The following day the heart was found to be enlarged to the anterior axillary line in the 6th intercostal space. A diastolic thrill was present at the base of the heart and a loud, high-pitched, musical murmur was heard over the entire precordium, loudest over the sternum at the level of the 3rd intercostal space. Crackling rales were audible over both lung bases posteriorly. The blood pressure was 140/70. The electrocardiogram showed evidence of left ventricular hypertrophy and myocardial damage. The Wassermann test was negative in both the blood and spinal fluid. With digitalis, bed rest, low-salt diet, and mercurial diuretics, the patient improved considerably and was discharged 15 days after admission. He was readmitted on Feb. 14, 1948, because of exhaustion resulting from hiccups of 7 days' duration. The physical findings were unchanged. The hiccups

FIG. 3.—(Rupture of aneurysm of an aortic cusp.) A glass rod can be seen passing through the ruptured aneurysm of the right anterior cusp. To the left of this is the intact aneurysm. A small portion of the commissure of the posterior aortic cusp shows a small rounded tear.

were controlled by quinidine on the day of admission. On the morning of Feb. 16 the patient became restless and stuporous, developed Cheynes-Stokes respirations, and expired.

The clinical diagnosis was syphilitic heart disease, syphilitic aortitis with aortic insufficiency and eversion of the right anterior leaflet, and congestive heart failure. Syphilis was considered to be the etiology despite the negative Wassermann reaction.

Necropsy Findings. The heart weighed 430 gm. The mitral valves were thickened and sclerotic. The leaflets of the aortic valve showed multiple fenestrations 1 to 3 mm. in diameter situated along the attachment of the valve to the aorta (Fig. 4). The right anterior leaflet had apparently been torn from its attachment to the aorta along both lateral margins. This resulted in an eversion of this leaflet and its vibration in the regurgitating column of blood. The aorta was smooth and there was no evidence of syphilitic aortitis.

FIG. 4. (Rupture of an aortic cusp.) The right anterior cusp (above numerals 8 to 10 on the scale) is torn at both commissures and lies flapped over into the left ventricle. The arrow points to several fenestrations which were present in the posterior cusp.

COMMENT. In this patient the eversion was the result of a severance of the tenuous attachment of the valve to the aorta, due to the increasing size of the fenestration which weakened the attachment of the valve on both lateral margins. It is of some interest that this patient was incorrectly considered to be an example of the typical variety of syphilitic aortic insufficiency with valve eversion, despite the negative Wassermann reaction.

CASE No. 5. F. Q., a 16-year old white girl, was admitted to this hospital on Aug. 27, 1941, with the following history: She was apparently in good health until March, 1941, when she developed a sore throat followed by severe migrating polyarthritis of all the large joints of the body. Her temperature ranged from 100 to 103 for a period of 4 weeks, and she lost 40 pounds in weight (from 168 to 128 lb.). In May, 1941, she was permitted to get out of bed but complained of dyspnea on exertion and of swelling of the ankles late in the day. The dyspnea increased in severity and she was referred to the hospital for admission. The pertinent findings on physical examination were: enlargement of the heart to the ante-

rior axillary line in the 6th interspace, a short systolic murmur heard at the apex, and a somewhat harsher systolic murmur heard at the aortic area; striking was a loud, high-pitched, musical diastolic murmur heard over the entire precordium, loudest in the 3rd interspace just at the left sternal border (Fig. 5). A diastolic thrill was palpable in this area. The electrocardiogram was within normal limits. The pulse was collapsing in nature and there were pistol-shot sounds in the femoral arteries. The blood pressure was 134/60. The lungs revealed no abnormalities on percussion and auscultation. The liver was enlarged and tender, and the edge was felt 3 fingerbreadths below the costal margin. Her course in the hospital was stormy and progressively downhill. The edema could not be controlled. She developed pericarditis 1 month after admission and an episode of digitalis intoxication with bigeminy at about the same time. The patient expired in congestive failure 10 weeks after admission. During all this time, the musical diastolic murmur and the signs of aortic insufficiency remained unchanged.

Necropsy. The heart showed mild, localized, fibrinous pericarditis. Active rheumatic pan-valvulitis was present with minimal change in the mitral valve. The aortic valve showed marked sagging of the right anterior cusp with moderate eversion of this leaflet, giving rise to aortic insufficiency. Microscopic examination revealed evidence of focal acute interstitial myocarditis, chronic endocarditis, and organizing pericarditis.

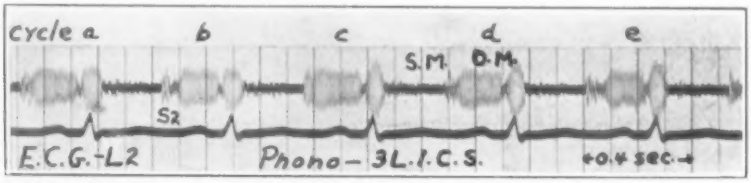

FIG. 5.—(Rheumatic aortic insufficiency.) The musical diastolic murmur has 2 distinct elements. The first element varies in onset from immediately after the second heart sound (cycle c) to 0.06 second after the second heart sound (cycle e). The first heart sound is buried in the second element of the musical diastolic murmur.*

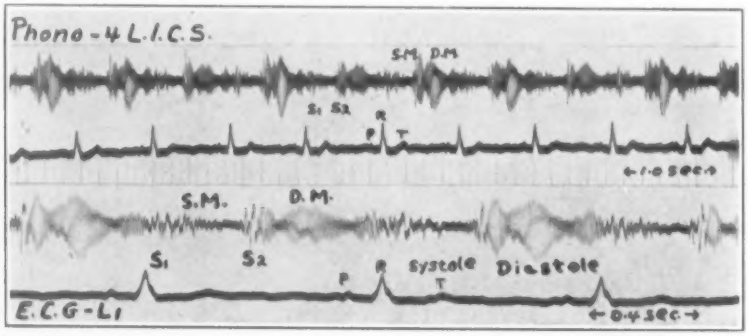

FIG. 6.—(Syphilitic aortic insufficiency.) There are 3 distinct crescendo-decrescendo elements to the diastolic murmur. This was thought to indicate retroversion of 2 aortic cusps.*

COMMENT. So far as we know, this is the only reported case in which a musical diastolic murmur with aortic insufficiency of rheumatic origin persisted until death, and in which necropsy examination was made. Again, the right anterior cusp was the one involved.

CASE No. 6. J. M. S., a 32-year old colored woman, was admitted to this hospital on Jan. 31, 1947, complaining of cough, expectoration of blood-tinged fluid, chills, and sweats of 3 days' duration. She was 6½ months pregnant at this time. Physical examination re-

* *Symbols:* S1, first heart sound; S2, second heart sound; S.M., systolic murmur; D.M., diastolic murmur.

vealed signs of right lower-lobe pneumonia which was confirmed by Roentgen examination. There were no clinical signs of cardiac abnormality at this time. The electrocardiogram was within normal limits. The blood pressure was 125/70. On Feb. 10, 1947, she went into labor spontaneously and delivered a living male child. The chest findings during this time were unchanged from those found on the initial examination. On Feb. 19, 1947, the patient complained of headache and stiffness of the neck, and rapidly became comatose. A spinal tap showed an increased pressure and cloudy spinal fluid. Culture of the cerebrospinal fluid revealed Pneumococcus Type XII, and this organism was also recovered from the blood stream. The patient was treated with penicillin intrathecally and intramuscularly, and with sodium sulfadiazine intravenously. By Feb. 25, 1947, some improvement was noted in her pneumococcic meningitis, and at this time a loud, high-pitched, musical diastolic murmur was heard over the entire precordium. Characteristic signs of aortic insufficiency were noted for the first time. The blood pressure at this time was 144/60. She continued to improve but the musical murmur persisted and was present upon discharge 9 weeks after admission. On Oct. 4, 1947, she was readmitted for a therapeutic abortion and at this time the murmur was still musical in nature. The heart showed slight enlargement but there was no change in her electrocardiogram. The blood pressure was 140/66. While following this patient in the out-patient department, it was noted in May, 1949, that the diastolic murmur was not musical, but the signs of aortic insufficiency were still present. This patient is still under observation; 2½ years after the onset of aortic insufficiency the heart is not greatly enlarged, the electrocardiogram shows little change, and she is free of symptoms.

Comment. This represents a case of acute bacterial endocarditis with the development of aortic valvulitis and aortic insufficiency, accompanied by a musical diastolic murmur. Although the diastolic murmur persisted, the musical quality disappeared after a period of 2 years.

Discussion. The Cause of Musical Aortic Diastolic Murmurs. The most typical cases of musical aortic diastolic murmurs are observed in the presence of syphilitic aortic regurgitation. In this condition there is observed a retroversion of the right anterior and sometimes other aortic leaflets. The right anterior (right coronary) cusp is the one most frequently involved. This may be due to the fact that the aorta in the region of the right anterior cusp receives little support from contiguous structures and that the column of blood in the aorta exerts its greatest force on the right anterior cusp. Occasionally, both the right anterior and the posterior (non-coronary) cusps are involved. The following factors might contribute to the retroversion: 1) the characteristic separation of the commissures which permits the free edge of the leaflet to sag, 2) a change in the fibrosa with loss of the compactly arranged collagen fibers and thickening of the leaflet by inflammatory tissue[4], 3) a loss of elastic tissue framework which helps support the leaflets[4]. The musical quality of the murmur apparently results from rapid vibration of the free edge of the valve by the regurgitant stream of blood.

In the other etiological types of musical diastolic murmurs, the mechanism and underlying pathology differ from those in patients with syphilitic aortic insufficiency. In bacterial endocarditis, the musical quality is the result of a vegetation vibrating freely in the blood stream. In the healed stage, it is probably the result of vibration of the thin peripheral portion of the healed vegetation acting like an everted leaflet. The disappearance of the musical quality is probably due to a breaking off of the vegetation or to gradual fibrosis of the edge of the valve with loss of the characteristic vibrating quality.

In the autopsied case with rheumatic fever, we observed sagging of the right anterior leaflet with slight eversion of its free portion. In the patients with rupture of the aortic leaflet, the ragged thin edge of the torn aneurysm of the right anterior cusp in one (Fig. 3) and

the torn right anterior leaflet in the other (Fig. 4) can be conceived to have vibrated rapidly in the regurgitant stream of blood. In order for a torn leaflet to give rise to a musical diastolic murmur, it is essential for the torn portion or the free edge of the valve to be reasonably thin and capable of vibrating freely in the blood stream. The combination of these factors is relatively rare in torn valves. We have encountered a number of valves where the edge had been torn from the main portion of the valve. In these a loud diastolic murmur and a marked thrill were present, but the musical quality of the murmur was lacking.

Effect of Retroversion on the Clinical Course. Retroversion of one or more aortic leaflets results in a sudden change in the circulatory dynamics. This results either in the precipitation of, or a marked increase in the degree of, aortic insufficiency. An added load is placed on the heart, the degree of which depends upon the previous condition of the heart muscle and the degree of aortic insufficiency. The sudden retroversion may precipitate an acute attack of left heart failure, shock, or coronary insufficiency and death. In the presence of pre-existing narrowing of the coronary orifices, the low diastolic pressure associated with the aortic insufficiency markedly decreases the degree of coronary filling and is an important factor in precipitating attacks of precordial pain and increasing the degree of heart failure. In many instances the patient may become gradually adjusted to the altered cardiovascular dynamics and to varying degrees of impairment in the cardiac reserve. In addition, a tremendous psychological factor is present in these patients who are conscious of the murmur.

Graphic Characteristics of the Murmur. The musical murmur is diastolic in time, is intense, and is high pitched. The pitch or frequency of the vibrations is greatest at the onset of the murmur (130 to 340 vibrations per second) and decreases in presystole (90 to 210 vibrations per second). The musical element usually starts 0.06 to 0.18 second after the second heart sound and rapidly reaches its greatest intensity in 0.02 to 0.06 second, following which there is a gradual decrescendo and a diminished frequency of vibrations.

The etiology of the murmur could not be determined by its time of onset with relation to the second heart sound, by the number of vibrations per second, or by the shape of the vibration as recorded in the phonocardiogram. The highest pitch was observed in R. H. (syphilis); the initial vibrations were 340 per second and the terminal vibrations 210 per second (Fig. 1). R. P. (rupture of aortic leaflet) had a high-pitched murmur (270–180), while F. K. (rupture of an aneurysm of aortic cusp) had the lowest pitch (130–130) which remained constant throughout diastole but became more intense in presystole. With J. M. S. (bacterial endocarditis), the murmur started with the second heart sound, but it also started with the second heart sound in R. H. (Fig. 1) (syphilis); in F. Q. (Fig. 5) (acute rheumatic fever) the onset of the murmur was observed immediately after to 0.07 second following the second heart sound.

The graphic representation of the murmur varied. E. B. (Fig. 6) (syphilis) showed 3 distinct crescendo–decrescendo elements. The first element was intense and high pitched (300 vibrations per second); the second, less intense and less high pitched (170 vibrations per second), seemed to have 2 components; and the third element was least intense and low pitched (100 vibrations per second). It was felt that this variation in vibration frequency and shape may have been due to in-

volvement of both the right anterior and posterior aortic cusps.

The underlying etiology of the murmur cannot be determined from the time of onset of the murmur with relation to the second heart sound and by its graphic representation in the phonocardiographic record. However, with the exception of one case with a torn aortic leaflet, the highest-pitched murmurs (maximal number of vibrations above 200 per second) were found in the patients with syphilitic aortic insufficiency.

Summary and Conclusions. There are reported 18 cases presenting the musical diastolic murmur of aortic insufficiency. Although syphilitic aortic valvulitis is by far the most frequent etiology, other causes are of considerable importance. The following etiologic factors are responsible for its production: 1) retroversion of an aortic leaflet associated with syphilitic aortic valvulitis (11 cases); 2) rheumatic aortic insufficiency (2 cases); 3) bacterial endocarditis (acute, 1 case; subacute, 2 cases); 4) rupture of an aortic leaflet (2 cases).

These patients were studied both clinically and by heart-sound records. They were kept under observation for variable periods, some for as long as 6 years. The clinical manifestations of this group of cases is discussed particularly from the standpoint of underlying etiology.

The prognosis in the patients with syphilitic etiology is not so grave as was considered to be the case in a previous report (1939).

The mechanism of the production of the musical murmur and its effects in altering the cardiovascular dynamics are discussed.

A description of the phonocardiographic records in the various etiologic groups is presented. The underlying etiology of the murmur cannot be determined by the time of onset of the murmur with relation to the second heart sound, or by its graphic representation in the phonocardiographic record. However, with the exception of one case with a torn aortic leaflet, the highest-pitched murmurs (maximal number of vibrations above 200 per second) were found in the patients with syphilitic aortic insufficiency.

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THE TREATMENT OF URGENT CASES OF PAROXYSMAL AURICULAR FIBRILLATION

A Proposed Method For Aiding in the Choice Between Digitalis and Quinidine

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The purpose of this report is to describe a group of cases of paroxysmal auricular fibrillation treated with a rapidly acting digitalis preparation and with quinidine and to discuss the most effective methods of treating this arrhythmia. Most of the cases were studied during an investigation of intravenously administered acetyl strophanthidin, a synthetic ester of the cardiac aglycone, strophanthidin.

Clinical Material and Method. During a period of 2 years 30 paroxysms of auricular fibrillation were observed in 25 patients, 2 patients being followed through 3 attacks each and 1 patient being followed through 2 attacks. The etiologic factors were as follows: No demonstrable causes, 3; cardiac, 9 (arteriosclerotic heart disease, 3; hypertensive heart disease, 3; rheumatic heart disease, 1; acute cor pulmonale [pulmonary embolus], 2); toxic and infectious conditions, 13.

In this last group the various underlying conditions found were as follows: pneumonia, diabetic acidosis, sequelae of catheterization of the urinary bladder, carcinoma of the larynx with sudden arterial occlusion of the right leg, terminal diffuse carcinomatosis, cerebral vascular accident, after-effects of hemorrhoidectomy and of prostatectomy, diffuse peritonitis, and fractured hip.

The ventricular rate was rapid in all cases, ranging from 140 to 210, and averaging 170. In all cases it was known that normal sinus rhythm had preceded the paroxysms. In each case the diagnosis of auricular fibrillation was confirmed electrocardiographically. Most of the patients received digitalis preparations followed by quinidine, as in Table 1.

Electrocardiograms were made just before treatment and at intervals of 1 to 2 minutes for 30 to 60 minutes following administration of an intravenous digitalis preparation, and then at intervals of 2 to 4 hours.

The doses used were as follows: ouabain, 0.5 mg.; acetyl strophanthidin, 1.2 mg.; digoxin, 1.5 mg., followed by 0.5 mg. 4 hours later; quinidine, 5-dose courses of 0.2 to 0.4 gm. every 2 to 4 hours, increasing by increments of 0.2 gm. in subsequent courses. Quinidine was administered orally in all cases.

Results. Effect of Intravenous Digitalis Preparations. Of the 27 paroxysms in which the initial treatment consisted of the intravenous administration of acetyl strophanthidin or ouabain, there was only 1 instance in which reversion to sinus rhythm was observed during the period of action of the drug. This was a 35-year old male without clinical evidence of heart disease who gave a history of previous paroxysms of auricular fibrillation lasting 24 to 48 hours. He received 0.5 mg. of ouabain 2 hours after the onset of the paroxysm, and 15 minutes later he had a sudden reversion to normal rhythm. There was, in addition, 1 instance in which auricular flutter with a varying 3:1 and 4:1 A–V block developed 13 minutes after the administration of acetyl strophanthidin to a pa-

tient in whom the paroxysm of auricular fibrillation occurred during cardiac catheterization.

In 26 of these 27 paroxysms intravenous digitalis preparations failed to produce any appreciable slowing of the ventricular rate. The single exception occurred in a patient with hypertensive heart disease and no apparent signs of heart failure. His ventricular rate slowed from 150 to 110 within 15 to 20 minutes after intravenous injection of 1.2 mg. acetyl strophanthidin.

Effects of Oral Digitalis Preparation. In the 18 paroxysms treated with oral digoxin, the results paralleled those obtained with the intravenous route in every case except one. The cardiac mechanism was not affected, nor was the ventricular rate slowed. The single exception was the case cited above in which intravenous administration of acetyl strophanthidin was followed by auricular flutter with a high grade of block. In this case, following oral digoxin, the flutter reverted to sinus rhythm.

Effect of Quinidine. In the 22 cases of paroxysm treated with quinidine, reversion to normal sinus rhythm was effected in 20. In most instances, reversion to a sinus mechanism occurred during the first or second course of quinidine therapy, when the individual dose had reached 0.4 to 0.6 gm. An individual dose of 0.8 gm. was necessary in only 1 case. However, the response varied; 1 paroxysm reverted after a single dose of 0.2 gm., while another required a total dose of 7.5 gm.

Spontaneous Remissions. In 8 instances no quinidine was given. One patient left the hospital before quinidine could be started. A second was in the terminal phase of diffuse carcinomatosis and was not given the drug. Both of these patients had been treated with digitalis previously without effect. In 5 other cases spontaneous remission occurred before quinidine therapy could be started. In 4 of these, previous digitalization was without effect. The fifth was the case mentioned above in which a flutter mechanism appeared after acetyl strophanthidin.

TABLE 1. TREATMENT PLANS OF 30 PAROXYSMS OF AURICULAR FIBRILLATION IN 25 PATIENTS

No. of paroxysms	*No. treated with intravenous digitalis preparations*	*No. treated with oral digitalis preparations*	*No. treated with quinidine*
11	11 (acetyl strophanthidin)		6 (following acetyl strophanthidin)
10	10 (acetyl strophanthidin)	10 (digoxin) following acetyl strophanthidin	8 (following acetyl strophanthidin and digoxin)
6	6 (ouabain)	6 (digoxin) following ouabain	6 (following ouabain and digoxin)
2		2 (digoxin)	2 (following digoxin)
1			1

Discussion. Digitalis. There is considerable difference of opinion regarding the action of digitalis in paroxysmal auricular fibrillation. The drug is said to perpetuate the arrhythmia[6,14,26,30], but this view is not substantiated clinically[10].

It is noteworthy that in only 1 of our cases could reversion to sinus rhythm be definitely attributed to digitalis action. In this case, sudden reversion occurred 15 minutes after administration of 0.5 mg. of ouabain. Reversion to a sinus mechanism occurred in 3 cases in this series following intrave-

nous administration of acetyl strophanthidin; in one, 5 hours later; and in the other two, 24 hours later. A study of this drug indicates that its duration of action is extremely short, the effects usually wearing off within 1 to 3 hours[11]. The reversion to normal rhythm in these 3 cases occurred after the drug had probably ceased to act and was, consequently, judged to be spontaneous. In a fourth paroxysm, combined treatment with intravenous acetyl strophanthidin and oral digoxin was followed by a change from auricular fibrillation to auricular flutter and then to normal sinus rhythm. Since these changes resembled quinidine action rather than digitalis effects, it is possible that they occurred independently of the digitalis preparations used.

Several reports mention the conversion of paroxysmal auricular fibrillation to normal rhythm during digitalis administration and ascribe the reversion to the action of the drug[12,13,31,34,37]. Analysis of these reports reveals that in almost every case conversion occurred from 2 to 11 days after the beginning of treatment. Only in the series reported by Fahr and LaDue[12] were there cases in which conversion occurred during the height of action of a digitalis preparation. In this connection, the tendency for this arrhythmia to undergo spontaneous reversion has often been stressed[10,25,27,30,34]. It is difficult, therefore, to determine whether reversions occurring during treatment with digitalis are directly attributable to the drug or are spontaneous[27,31,38].

The effectiveness of digitalis in slowing the ventricular rate in cases of paroxysmal auricular fibrillation is questionable. It has been advocated that the drug be given in all cases with rapid ventricular rate in order to slow the rate of the ventricles[9,12,19,25,35]. However, it is often ineffective. Wyckoff and Goldring[46] found that the dose of ouabain necessary to produce a therapeutic effect was higher in 7 patients with fever than in 21 patients with normal temperature. Similar observations are reported by others[17,30]. A case has been reported in which a toxic ventricular arrhythmia appeared before any ventricular slowing occurred after intravenous digitoxin[28]. Obviously, the presence of heart failure calls for treatment with digitalis, regardless of the rate of the ventricles and regardless of whether the fibrillation is chronic, of recent origin, or paroxysmal. It is commonly observed that in such cases not only is the decompensation improved but the ventricular rate is slowed. It is in the absence of heart failure that the drug is generally without effect on the rate of the ventricles[27,30].

Quinidine. In the 20 paroxysms which reverted to normal rhythm with quinidine, it is possible that reversion was spontaneous in 2, since normal rhythm appeared within 4 hours after single doses of 0.2 gm. and 0.4 gm. of the drug, respectively.

There is general agreement that where specific treatment for paroxysmal auricular fibrillation is indicated, the use of quinidine to restore the rhythm to normal is the treatment of choice[4,5,14,15,18,24,43], although some still recommend that its use be confined to cases without heart disease[7,43].

Earlier reports placed the incidence of conversion of chronic auricular fibrillation to sinus rhythm with quinidine at 60 to 75%[19,26,41]. More recently, however, the use of larger doses has resulted in conversion in over 80% of such cases[21,29,39]. In paroxysmal auricular fibrillation the incidence of conversion has been considerably higher, 85 to 100%[21,22,32,39]. Recent reports on blood quinidine concentration and its correlation with clinical effects may point the way to even greater efficiency in the use of the drug[21,39].

Indications For Specific Therapy.

An underlying etiologic factor was present in 22 of the 25 patients in this series. While demonstrable heart disease was present in only 9 of the cases, most of the patients were in the older age group, the average age being 62 years. It is possible that arteriosclerotic heart disease was present in some cases, despite the absence of clinical signs. On the other hand, the incidence of toxic and infectious factors was unusually high, 13 of 25 patients having this complication.

The indications for specific therapy in paroxysmal auricular fibrillation vary with the duration and frequency of the attacks and with the nature of the underlying condition. It is commonly felt that paroxysmal auricular fibrillation is a mild disorder with a remarkable tendency to spontaneous reversion. Hence, general measures should be employed before any specific therapy is instituted, at least in those cases where neither heart disease nor circulatory embarrassment is present[5,15,25,31]. However, statistical studies show that 85% of paroxysms occur in patients with heart disease, and that toxic and infectious conditions provide the necessary stimulus in an additional 6%. Thus, of cases of this arrhythmia, only 9% occur in individuals with normal hearts[34]. It has been stated that paroxysmal auricular fibrillation may be of allergic origin[20]. In such cases, quinidine allergy might also have to be reckoned with.

There is general agreement that the onset of auricular fibrillation does not materially affect the natural progress of the underlying heart disease[8,22,41,45]. Nevertheless, the development of the arrhythmia may add to the cardiac insufficiency[1,23,29,34,35]; and speed may become an important consideration in treatment, particularly if the ventricular rate is rapid[17,37]. It seems justifiable to conclude, therefore, that the onset of paroxysmal auricular fibrillation in a patient with heart disease calls for immediate institution of measures designed to control the arrhythmia, particularly if the ventricular rate is rapid. We believe that a similar urgency exists in toxic or infectious cases where the arrhythmia, with rapid ventricular rate, arises in a patient who is already seriously ill as a result of his underlying disease.

Proposed Method for Management of Urgent Cases. Most of the patients comprising this series were seriously ill, and it was felt that the onset of the arrhythmia, with rapid ventricular rate, added to the gravity of the prognosis. It was urgent to determine the proper therapeutic agent in each case, and it seemed plausible to start with intravenous digitalis preparations, since their effects can be judged within a fraction of an hour. Oral digoxin or quinidine effects, however, could easily be delayed for many hours. Our experience indicates that ours was a proper course and, in principle, it might well be applied to a broader group of cases.

It is proposed, therefore, that in cases of auricular fibrillation with rapid ventricular rate, particularly where urgency exists because of associated conditions, a plan of treatment be employed which, since it includes the use of both digitalis and quinidine, can be applied in all urgent cases, regardless of whether the arrhythmia be paroxysmal, of recent origin, or chronic. The method is:

A. Begin treatment with the intravenous administration of a rapidly acting digitalis preparation. In view of the high incidence of toxic manifestations encountered with acetyl strophanthidin, it is recommended that ouabain, k-strophanthin, lanatoside C or digoxin be used instead.

B. If slowing of the ventricular rate occurs, digitalization may be

quickly accomplished, as in several recently proposed methods for the combined use of intravenous and oral digitalis preparations[2,3,16].

C. If, however, slowing of the ventricular rate does not follow within 20 to 60 minutes, depending upon the latent period of the preparation used, quinidine therapy should be initiated without delay. If congestive failure is present, digitalis should be continued.

Summary and Conclusions. 1. Twenty-five patients with 30 paroxysms of auricular fibrillation were treated with rapidly-acting intravenous digitalis preparations, oral digoxin, and quinidine in various combinations.

2. Digitalis preparations did not restore normal rhythm or slow the ventricular rate except in the one case in which regular sinus rhythm was restored.

3. Quinidine converted 20 of 22 paroxysms to normal rhythm, after digitalis had failed to slow the ventricular rate.

4. The following method of treatment is proposed for urgent cases of auricular fibrillation:

(a) Begin treatment with a trial of a rapidly-acting intravenous digitalis preparation.

(b) If slowing of the ventricular rate occurs, continue digitalization.

(c) If slowing of the ventricular rate does not result, institute quinidine therapy without further delay.

(d) If congestive failure is present, continue digitalis in conjunction with quinidine.

ADDENDUM: Since the writing of this report 4 additional cases have been managed according to the method described above. One reverted to normal sinus rhythm 30 minutes after 1.5 mg. of digoxin was administered intravenously. The other 3 received 0.5 mg. ouabain intravenously without effect and then subsequently reverted to regular sinus rhythm with quinidine.

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THE VASODILATOR EFFECTS OF PRISCOLINE IN PATIENTS WITH ISCHEMIC EXTREMITIES*

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This investigation was undertaken to study, under standard conditions, the cardiovascular responses to priscoline of patients having peripheral vascular disease. Priscoline has been shown to have sympatholytic properties[3]. We had already demonstrated a selective effect on digital cutaneous blood flow in normal subjects[2].

The patients studied consisted of 16 males and 4 females, ranging in age from 17 to 78 years. Fourteen had arteriosclerosis, among whom 1 also had diabetes mellitus; 4 had thromboangiitis obliterans; 1 had Raynaud's disease; and 1 had severe vasospasm with distal arterial occlusion secondary to spina bifida. Individual diagnoses are listed in Table 1.

Control subjects were nine healthy males ranging in age from 21 to 43 years. The results of the study of this group of normal individuals have been previously reported[2]. Both the control group and the group reported here were studied under identical circumstances except for the time of year, the former being studied between March and July, the latter between September and March.

In order that the vasodilator effect of priscoline could be compared with a standard, vasodilatation tests were performed in each case to determine approximately the maximal capacity for blood flow to the toes. In addition, basal vascular tone tests[5] were performed in each case, with the thought that the effects of the drug might be related to the inherent cutaneous vascular tone of the patient.

Methods. Effects of Priscoline. Patients were tested at least 4 hours after having food, drink, or a hot bath or shower. Prior to the test they were allowed to rest for about half an hour in a comfortable environment. At the start of the test they were placed in a constant temperature room at 23°C. This temperature was chosen because it usually produces vasoconstriction of the digital vessels and is not severe enough to overwhelm the

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TABLE I.—VASODILATOR EFFECTS OF PRISCOLINE IN 20 PATIENTS WITH VASCULAR DISEASE

No.	Subject	Age	Sex	Wt., lbs.	Diagnosis*	Dose, mg.	Pulse Rate				Blood Pressure				Cardiac Output				Digital Cutaneous Blood Flow *Before*			
								Time				*Time*				*Time*							
							Before	Max. change	Max. change	Dur. Avg. change	Before	Max. change	Max. change	Dur. Avg. change	Before	Max. change	Max. change	Dur. Avg. change	L. finger	L. toe	R. finger	R. toe
1	V. C.	24	F	48	R. D.	40	68	72	2	40'	108/64	108/60	N	N	12	5	N	N	6	3		
2	J. R.	45	M	76	A. S.	50	52	84	2	60	122/72	160/80	60	90'	16	38	40	60	20	2		3
3	J. S.	17	F	52	S. B.	40	84	98	1	5	115/75	108/64	N	N	30	7	38	38	2	7		2
4	M. H.	68	M	58	A. S.	40	72	82	2	70	144/86	125/80	15	115'	0	50	5	115'	3	4	3	4
5	G. S.	71	M	82	A. S.	50	60	90	5	98'	192/105	208/105	92	98'	Incalculable				67	3	—	2
6	H. H.	71	M	52	A. S.	50	63	93	30	30'	130/77	165/80	8	40'	11	91	28	40'	4	3		14
7	A. G.	54	F	63	A. S.	50	86	140	1	37'	109/70	140/70	17	37'	6	47	1	30'	3	14	4	37
8	B. B.	55	M	55	T. O.	50	84	96	2	26	168/90	190/102	10	14'	60	65	N	N	35	7	28	12
9	E. E.	73	M	55	A. S.	40	76	120	2	80	118/82	132/90	17	80'	58	66	N	N	5	2	8	1
10	J. McC.	69	M	52	A. S.	30	62	84	22	45	114/78	138/86	62	82'	8	61	67	82'	3	2	3	A
11	F. L.	71	M	81	A. S.	50	64	92	1	41	191/110	208/100	1	14'	34	50	44	44	33	2	55	3
12	W. F.	66	M	63	A. S.	40	68	84	2	44	180/85	158/78	35	35'	18	44	12	15	4	12	6	21
13	J. H.	70	M	76	A. S.	50	76	96	5	25	137/84	183/85	30	32'	22	12	15	15	10	10	12	6
14	A. G.	78	M	50	A. S.	40	56	72	65	65'	142/78	122/74	15	55	38	60	50		5	3	4	3
15	J. H.	61	F	66	A. S.	50	68	84	7	47'	116/65	130/70	17	47'					4	2	10	10
16	J. D.	45	M	86	T. O.	50	62	68	40	55'	118/82	132/92	40	40	42	30	10	30	19	20	1	15
17	A. McF.	50	M	70	A. S.	50	68	80	20	15	112/75	130/72	12	15	2	34	12	60'	2	1	3	1
18	A. McC.	39	M	70	T. O.	50	68	80	12	35	120/78	114/78	15	50					7	9	5	4
19	N. A.	63	M	62	A. S.	50	84	96	3	60'	142/80	174/90	60	60'	24	52	5	40	7	2	7	2
20	J. D.	33	M	74	T. O.	50	58	80	5	35	124/90	130/88	5	65'					33	15	46	12
	Averages						69	90	13		133/78	151/81	30		2	29	22	—	15	6	13	7

KEY FOR TABLE 1.

Digital cutaneous blood flow expressed in cc. 100 cc. tissue/minute.
All times in minutes. All studies made between September and March.

N: change not significant
+: change still apparent at termination of experiment
—: determination not made
C. O.: cardiac output in % of normal
R. D.: Raynaud's disease
A. S.: arteriosclerosis
S. B.: spina bifida with secondary arterial insufficiency
T. O.: thromboangiitis obliterans
A: extremity amputated

*Diagnoses

1. Raynaud's disease with infected right index finger.
2. Arteriosclerosis with occlusion left popliteal artery.
3. Spina bifida with distal arterial occlusion and ulceration of right toes.
4. Arteriosclerosis with occlusion of right and left popliteal arteries and ulceration of left 2nd and right 1st and 4th toes.
5. Arteriosclerosis with bilateral popliteal occlusion.
6. Arteriosclerosis with occlusion of the left posterior tibial and the right posterior tibial and dorsalis pedis arteries. Necrosis of right 5th and right great toes.
7. Diabetes mellitus. Arteriosclerosis with bilateral popliteal thrombosis and necrosis of right 4th toe.

TABLE 1. (*Continued*)

Table 1, cont'd	Digital Cutaneous Blood Flow												Changes Induced								
	Max. change				Max. change time				Duration any change							Blood flow					
No.	L. finger	L. toe	R. finger	R. toe	L. finger	L. toe	R. finger	R. toe	L. finger	L. toe	R. finger	R. toe	Pulse	B. P.	C. O.	L. finger	L. toe	R. finger	R. toe	Body temp. C.	Tone, tone
1	6	3	—	—	N	N	—	—	N	N	—	—	↑ 4	0/↑4	↑ 7	0	0	—	—	↑0.1	High
2	35	22	—	5	18	80	—	8	90↑	90↑	—	80	↑32	↑38/↑8	↑22	↑15	↑20	—	↑ 2	↑0.2	Low
3	24	9	—	3	8	8	—	8	58↑	58↑	—	58↑	↑14	↑7/↑11	↑23	↑22	↑ 2	—	↑ 1	↑0.2	High
4	3	12	4	8	N	35	N	35	N	115↑	N	115↑	↑10	↑19/↑6	↑50	0	↑ 8	↑ 1	↑ 4	↑0.1	High
5	120	27	—	10	37	92	—	92	98↑	86	—	98↑	↑30	↑16/0	—	↑53	↑24	—	↑ 8	↑0.2	Low
6	3	5	—	21	N	N	—	29	N	N	—	40↑	↑30	↑35/↑2	↑80	↑ 1	↑ 2	—	↑ 7	↑0.3	High
7	3	21	6	43	N	32	27	15	N	37↑	37↑	37↑	↑54	↑31/0	↑53	0	↑ 7	↑ 2	↑ 6	↑0.3	High
8	51	19	30	16	14	35	N	4	35	44↑	N	44↑	↑12	↑22/↑12	↑ 5	↑16	↑12	↑ 2	↑ 4	↑0.2	Low
9	15	22	16	29	12	67	12	72	32	80↑	40	80↑	↑44	↑34/↑8	↑ 8	↑10	↑20	↑ 8	↑28	↑0.6	High
10	5	8	6	A	12	62	15	A	35	82↑	82↑	A	↑22	↑24/↑8	↑53	↑ 2	↑ 6	↑ 3	A	↑0.6	High
11	45	46	78	48	3	44	24	44	15	44↑	44↑	44↑	↑28	↑14/↑15	↑84	↑11	↑44	↑23	↑45	0.5	Low
12	6	12	7	19	N	N	N	N	N	N	N	N	↑16	↑22/↑7	↑32	↑ 2	0	↑ 1	↑ 2	0.2	Low
13	13	7	23	8	10	15	15	10	10	15	15	10	↑20	↑46/↑1	↑36	↑ 3	↑ 3	↑11	↑ 2	0.3	Low
14	9	6	11	8	15	10	55	55	65↑	65↑	65↑	65↑	↑16	↑20/↑4	↑22	↑ 4	↑ 3	↑ 7	↑ 5	0.2	High
15	2	2	4	2	10	N	50	10	10	N	50↑	10	↑16	↑14/↑5	—	↑ 2	0	↑ 2	↑ 8	↑0.1	High
16	6	20	0	20	20	10	N	20	65↑	N	N	20	↑ 6	↑14/↑10	—	↑13	0	0	↑ 5	↑0.1	Low
17	4	3	13	4	5	20	5	20	40	60	60	52	↑12	↑18/↑3	↑32	↑ 3	↑ 2	↑10	↑ 3	↑0.2	High
18	17	15	10	5	5	55	30	30	25	55↑	5	5	↑12	↑6/0	—	↑10	↑ 6	↑ 5	↑ 1	↑0.3	Low
19	38	22	30	9	5	30	17	40	60↑	60↑	60↑	60↑	↑12	↑32/↑10	↑28	↑31	↑20	↑23	↑ 7	↑0.5	High
20	12	32	35	32	50	45	43	5	65↑	65↑	65↑	65↑	↑22	↑16/↑2	—	↑21	↑17	↑11	↑20	↑0.3	Low
Averages	21	16	16	16	15	37	27	28	—	—	—	—	↑21	↑18/↑3	↑27	↑ 6	↑10	↑ 3	↑ 9	↑0.3	

Key for Table 1. (*continued*)

Diagnoses (*continued*)

8. Thromboangiitis obliterans with occlusion right and left dorsalis pedis arteries and right radial and ulnar arteries and necrosis of right 2nd toe.
9. Arteriosclerosis with occlusion right and left dorsalis pedis and posterior tibial arteries, and right and left ulnar arteries.
10. Arteriosclerosis with amputated right leg and occlusion of left dorsalis pedis and posterior tibial arteries.
11. Arteriosclerosis with occlusion of right and left dorsalis pedis arteries.
12. Arteriosclerosis with occlusion of right popliteal and left dorsalis pedis and posterior tibial arteries and necrosis of right great toe.
13. Arteriosclerosis with bilateral popliteal occlusion.
14. Arteriosclerosis with bilateral popliteal occlusion.
15. Arteriosclerosis with bilateral popliteal occlusion and necrotic lesion above right internal malleolus. Erysipeloid of Sulzberger.
16. Arteriosclerosis or thromboangiitis obliterans with occlusion of right popliteal artery and left dorsalis pedis and posterior tibial arteries.
17. Arteriosclerosis with occlusion of the abdominal aorta.
18. Thromboangiitis obliterans with necrosis of left 1st toe and occlusion of left dorsalis pedis and right posterior tibial arteries.
19. Scleroderma and arteriosclerosis with bilateral popliteal occlusion.
20. Thromboangiitis obliterans with occlusion of left ulnar artery and necrosis of left 3rd finger.

opposite effect of a drug. The subject was supine on a ballistocardiographic table of the Starr type[7] clad only in a light hospital gown; thermocouples (copper–constantan) were attached to the left and right third finger, and to the left and right first toe, unless these digits were missing, in which case an adjoining digit was used. Readings of skin temperature, pulse rate, and blood pressure were recorded every 5 minutes, ballistocardiograms approximately every 15 minutes, and respiration and mouth temperature approximately every 20 minutes. A steady state was arrived at about ½ hour after the start of the test, and was maintained for 20 to 25 minutes, at which time 30 to 50 mg. of priscoline (depending upon the patient's body weight) were injected intravenously. Following the administration of the drug observations were continued for ½ hour or more.

Reflex Vasodilatation in Response to Heat Applied to the Trunk[1]. The vasodilatation test was performed on a different day. A meal was allowed. Room temperature was maintained at 20°C. in order that the result of the vasodilatation test would be comparable with previously established normal standards of blood flow to the extremities made at this room temperature. Two 60-watt electric pads at "medium" heat were applied to the trunk of the patient clad in a light hospital gown. The trunk and upper extremities were covered with a sheet and two heavy woolen blankets extending from the neck to the ankles. Thermocouples were placed on the first and third toes of the right and left feet, which were exposed. No measurements of finger temperature were made since none of the upper extremities had occlusive arterial disease. The heat to the body was maintained until no further reflex vasodilatation in the toes could be produced. For clarity, and in order to make comparisons with previous data, skin temperature data were converted to cubic centimeters of blood flow per 100 cc. of digit per minute by a relationship previously established[4].

Since our only interest in the patient's response to heat was to determine "maximum" capacity for peripheral blood flow, no readings of cardiac output, blood pressure, and pulse rate were made during this preliminary vasodilatation test.

Basal Vascular Tone. Peripheral vascular tone was determined according to the method described by Naide and Sayen[5]. The patient is placed in a basal condition in a room at 20°C. and the skin temperature of the fingers is measured. At the end of a 15-minute period those individuals whose finger skin temperature is below 25°C. are recorded as having a "high peripheral vascular tone", those with skin temperatures at or above 25°C. are recorded as having a "low tone".

TABLE 2.—PER CENT CHANGES IN CUTANEOUS BLOOD FLOW IN TOES, CARDIAC OUTPUT, PULSE RATE, AND BLOOD PRESSURE AS A RESULT OF INTRAVENOUS PRISCOLINE

	Ischemic group	*Control group*
Individuals in whom priscoline significantly increased cutaneous blood flow in the toes	80%	67%
Increase of cutaneous blood flow in toes (average for all cases)	150%	150%
Increase of cardiac output (average for all cases)	28%	6%
Increase of pulse rate (average for all cases)	28%	18%
Increase of blood pressure (average for all cases): Systolic	12%	18%
Diastolic	4%	9%

Results. Cutaneous Blood Flow. A high percentage of individuals with and without peripheral arterial disease showed satisfactory digital cutaneous vasodilatation following the administration of intravenous priscoline. Table 2 shows that the results are more satisfactory in this respect in ischemic toes than in normal toes. There was no significant difference between the increments in flow in the fingers of the control group (normals) and the fingers of the group with ischemic lower extremities. It is noteworthy that at the start of the test the patients as

a group had a consistently higher average flow to the fingers than did the controls. This was particularly true of patients having "low vascular tone".

BLOOD PRESSURE. A significant rise in systolic blood pressure generally followed the intravenous administration of priscoline, averaging 18 mm. Hg in the ischemic group and 18 mm. Hg in the controls. The individual blood pressure response, however, was unpredictable, varying from a rise of 46 mm. Hg of systolic pressure to a drop of as much as 22 mm. Hg.

CARDIAC OUTPUT. There was a definite increase of cardiac output which seemed to depend largely on an increase of pulse rate. This contrasts with the group of normal controls which showed insignificant change of cardiac output with the significant increase in pulse rate. We have no explanation for this.

RESPIRATION. No significant changes in respiration were noted at any time.

TEMPERATURE. An average decrease of 0.3°F. was noted in mouth temperature. As in the case of the controls, this varied with the amount of vasodilatation.

INFLUENCE OF VASCULAR TONE. No relationship between basal vascular tone and the response to the drug could be demonstrated.

SIDE EFFECTS. In every patient, injection of priscoline caused some flushing of the face and injection of the conjunctivae. The majority of patients complained of chilly sensations along the spine following administration of the drug; 5 of these shivered. The most severe subjective symptoms were experienced by the Patient 11. He had the greatest vasodilator response in the skin of the toes. This patient also experienced very unpleasant palpitation. One patient with bronchial asthma, not included in the series, tolerated the drug well without pulmonary symptoms. A patient in mild congestive failure showed no unfavorable reaction to priscoline.

Discussion. It is interesting to note that priscoline appears to be a more potent vasodilator in ischemic digits than in normal, as evidenced by the greater percentage of "maximal" (vasodilatation test) flow, and by the greater quantitative increment in flow, attained in the ischemic group than in the normal (see Table 3). One can only speculate on the reason for this. Since we found no relationship between basal vascular tone and response to the drug, and since we have previously shown in dogs that the vasodilator action of priscoline is local rather than central[6], we are drawn to the hypothesis that the drug may have a more profound local action on blood vessels in ischemic tissue than on those in normal tissue.

Apparently the priscoline effect is fairly selective of cutaneous vessels in these patients as well as in the normals. There were, as a rule, only small changes in blood pressure and cardiac output in the majority of cases, which leads us to believe that vasodilatation with priscoline was not conspicuous elsewhere.

Summary. 1. The effect of intravenous priscoline on digital cutaneous blood flow, cardiac output, pulse rate, mouth temperature, and respiration was studied in a group of 20 patients with peripheral arterial disease. The results of these studies were compared with an equivalent study of normal individuals, previously reported.

2. The patient's "maximum" blood flow in the periphery was determined by vasodilatation in response to a combination of reflex heat and a meal. "Maximum" flow was correlated with the flow obtained by priscoline.

3. The "basal vascular tone" of each patient was determined.

4. Priscoline was more effective in increasing digital cutaneous blood flow

TABLE 3.—FINAL BLOOD FLOW IN SKIN OF DIGITS AFTER PRISCOLINE AS COMPARED TO THAT AFTER HEAT APPLIED TO THE TRUNK (C.C./100 C.C. OF DIGIT/MINUTE)

		Ischemic group		*Controls*	
		Priscoline	*Heat*	*Priscoline*	*Heat*
BLOOD FLOW TO SKIN OF DIGITS IN CC./100 CC./MINUTE	Fingers	19	100±	17	100±
	Toes	16	32	5	100±

100± cc./100 cc./minute is assumed to be the approximate maximal digital cutaneous blood flow in a normal extremity. For *increments* see Table 1. For % increases above initial levels see Table 2.

in patients with arterial disease than in the normal controls.

5. In our patients the digital cutaneous blood flow produced by priscoline was about half of that produced by a combination of food and heat.

6. The increase in flow was, in most instances, still apparent at the termination of the test, 40 to 115 minutes after the administration of the drug.

7. There was no relationship between the effect of priscoline and "basal vascular tone".

8. There was little change in cardiac output and blood pressure, except in a few drug sensitive individuals. This, again, suggests a fairly selective action of priscoline as a (digital) cutaneous vasodilator.

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DIGITAL CUTANEOUS BLOOD FLOW, CARDIAC OUTPUT, BLOOD PRESSURE AND PULSE RATE IMMEDIATELY FOLLOWING THE ADMINISTRATION OF FOUR POTENTIAL VASODILATORS*

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In our search for an "ideal" peripheral vasodilator, one which would cause maximal blood flow through the skin of the fingers and toes with minimal changes of the circulation elsewhere, certain substances recommended themselves to us for various reasons: 1) Dioxyline phosphate (paveril-phosphate) hereinafter referred to as L 08146† was tried because it is a papaverine-like substance. 2) N-Phenoxyisopropyl-n-benzyl-β-chlorethylamine hydrochloride, hereinafter referred to as SKF 688A†, was tried because it is a dibenamine-like substance. Both papaverine[3] and dibenamine[4] are known to be vasodilators. 3) It was considered possible that sodium salicylate might derive some of its antipyretic properties from peripheral cutaneous vasodilatation. 4) ACTH was tried because it is known to produce profound physiological changes. Its actions on the vascular system are relatively unknown, although increases in blood pressure have been recorded after several days of therapy[5].

Method. The subjects used in these studies were either normal adults or patients with mild or moderately advanced peripheral arteriosclerosis, and, in the case of ACTH, early to moderately advanced scleroderma. None had fever. Their ages were between 24 and 61. Except in the case of ACTH, approximately half of the subjects receiving each drug were normal adults. Each subject was studied by a system outlined by us previously[2,6]. In the case of SKF 688A, the drug was administered orally 1½ hours before the experiment was started. Two hours was thought to be the time of maximum action of this drug when so administered[1]. The changes induced by the drugs were compared to those in a group of normal controls previously studied by us, each of whom was given a placebo injection. When drugs were administered parenterally, the subjects were observed for from 1 to 2 hours.

Results. As can be seen in Table 1, no significant effect was produced by these drugs on digital cutaneous blood flow, cardiac output, blood pressure, or pulse rate during the 1 to 2-hour

* This is the second of three papers on the general topic of the effect of certain drugs on peripheral cutaneous blood flow, blood pressure, and cardiac output. They are published together because of their interdependence.

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TABLE 1. EFFECT OF 4 DRUGS ON CARDIOVASCULAR SYSTEM OF 19 SUBJECTS

	No. of experiments	Mode of administration	Average dose	Mean changes induced: Cardiac output	Pulse rate	Blood pressure	Body temp. °C.	Mean changes induced Blood flow cc./100 cc./min.: Finger	Toe	Maximum induced cc./100 cc./min.: Finger
Controls (normals, untreated)	6	*	*	−4	−4	−2 +8	−0.2	−1	−2	2
ACTH	4	I. M.	75 mg.	−7	−5	0 +3	−0.1	+1	−2	2
SKF 688A	6	P. O.**	100 mg.	−6	−1	+3†	−.05	−3	−2	2
L 08146	5	I. V.	90 mg.	0	−1	−1 −3	−0.2	−6	0	2
Sodium salicylate	4	I. V.	1.8 gm.	−9	0	+3 0	−0.2	+1	0	3

* Placebo injected subcutaneously.
† Symptoms of orthostatic hypotension were often present at the termination of the experiment.
** Drug administered orally in the form of 2—4 tablets of 37.5 mg. each 1½ hr. before observations.

period in which the subjects were observed.

Statistical observation of these data makes it extremely improbable that any further study of any one of these drugs would be likely to change the results. It is even more unlikely that any one of these drugs would be comparable to priscoline[2,6] or alcohol[2,3] as a vasodilator.

Conclusion. SKF 688A, L 08146, sodium salicylate, and ACTH, in the doses mentioned above, have no immediate measurable effects on digital cutaneous blood flow, cardiac output, blood pressure, pulse rate or mouth temperature.

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MEASUREMENTS OF CERTAIN CARDIOVASCULAR RESPONSES TO ACTH AND CORTISONE IN MAN*

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The wide use of ACTH and cortisone in a variety of conditions made it desirable to observe objectively some cardiovascular responses in a group of individuals being treated with these drugs. We had failed to induce peripheral vasodilatation by a single therapeutic injection of ACTH during a two-hour period of observation[4]. Perera noted a moderate rise in blood pressure after several days of treatment with ACTH or cortisone[3].

In the present study observations were made of digital cutaneous temperature, as an index of blood flow, cardiac output, blood pressure, pulse rate, and mouth temperature, on a group of patients diagnosed as having rheumatoid arthritis. The fact that they were hospitalized made it possible to control the conditions under which the studies were performed and to make daily observations of comparative value.

Method. Eighteen patients with rheumatoid arthritis, 15 females and 3 males, ranging in age from 19 to 58, were studied before and during therapy with ACTH and cortisone. Studies of each patient were made almost daily for from 6 to 15 days. Each patient was studied between 8 and 10 a. m. Food, medication, and hot baths were withheld for a period of at least 4 hours prior to each study. The subject was supine in a constant temperature room at 20°C. This temperature has been used by us previously[2] as a standard vasoconstrictor stimulus. At the end of fifteen minutes determinations were made of cutaneous temperature of fingers and toes, blood pressure, pulse rate, mouth temperature, and (in all but 3 cases) cardiac output by a ballistocardiograph of the Starr type[5]. After 1 to 4 control studies were performed, either ACTH (400 to 1150 mg.) or cortisone (400 to 700 mg.) was given in equally divided doses (see Table 1). During the period of drug administration the studies were repeated.

While the patients were in the hospital, they were being observed also by others[1] for changes in knee joint fluid, changes in joint temperature, and clinical improvement in their arthritic condition.

Results. The cardiovascular changes found are shown in Table 2. The following changes occurred after several days of therapy:

* This is the third of three papers on the general topic of the effect of certain drugs on peripheral cutaneous blood flow, blood pressure, and cardiac output. They are published together because of their interdependence.

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TABLE 1. TREATMENT OF 18 CASES OF RHEUMATOID ARTHRITIS

	Control period	*Period of treatment*
Day of hospitalization	1 2 3 4 5	6 7 8 9 10 11 12 13 14 15
No. of observations	1 to 4 0	4 to 6
Amount drug given	0	300 mg. 1st day (100 mg. daily thereafter) cortisone or 400–1150 mg. (av. 100 daily) ACTH in equally divided doses

TABLE 2.—AVERAGE MAXIMAL CHANGES INDUCED WITH CORTISONE AND ACTH

	Temp. of fingers °C. Mean	*Temp. of toes °C. Mean*	*Cardiac output C_c*	*Systolic blood pressure mm.Hg*	*Diastolic blood pressure mm.Hg*	*Pulse rate/min.*	*Mouth temp. °C.*
CORTISONE (7 patients)							
Mean change in all patients	+.5	+.3	−15	0	−2	−8	+.06
Standard deviation of mean group change	.1	.5	.5	3	4	2	.06
ACTH (11 patients)							
Mean change in all patients	+3.2	+1.1	−31	+3	0	−24	−.49
Standard deviation of mean group change	.9	.5	10	4	3	4	.12

1. An increase of the temperature of the fingers of the group receiving ACTH. This occurred in 7 of 11 patients. Vasodilatation did not occur in the toes of the majority (9 out of 11) of the patients. No significant vasodilatation occurred in patients receiving cortisone.

2. A decrease in cardiac output, particularly in the group receiving ACTH. This was largely dependent on a decrease in pulse rate.

3. A decrease of mouth-temperature in the group receiving ACTH.

Discussion. In these patients with rheumatoid arthritis, ACTH and cortisone afforded considerable subjective and objective improvement, with decrease in body temperature, and lessening of pain. It is hardly surprising that there occurred a decrease of pulse rate and concomitant decrease in cardiac output, without change in stroke volume. A somewhat more striking therapeutic effect was obtained in the patients receiving ACTH than in those receiving cortisone. A significant increase in digital skin temperature resulted in those receiving ACTH, but not in those receiving cortisone. We do not know how ACTH induces vasodilatation in these cases. The vasodilator action may result from the relief of pain and from the relief of vasoconstriction resulting from pain, or from some direct vasodilator effect.

Perera demonstrated that ACTH or cortisone caused a moderate rise in blood pressure of hypertensives and of normotensives having rheumatoid arthritis[3] and related disorders. We do not know why our group of patients did not have any significant blood pressure changes.

Summary. The only remarkable circulatory effect of ACTH therapy in a group of patients with rheumatoid arthritis was an increase in temperature of the fingers, apparent within several days. This did not occur in patients receiving cortisone. The vasodilatation may have resulted from effects of ACTH, either directly on the vessels, or on their autonomic control, or, indirectly, on disease factors that had caused excessive vascular tone.

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THE PRODUCTION OF URINARY CASTS DURING THE USE OF CATION EXCHANGE RESINS*

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Cation exchange resins, which are being used in laboratory[1,2,10] and clinical studies[3,5,7-9,12], are polymers having hydrogen or ammonium ions attached to sulfonic acid or carboxylic acid polar groups. These resins have the capacity of exchanging their hydrogen or ammonium ions for other cations with which they may come in contact. In addition, they also have the capacity of combining with other substances such as alkaloids, thiamin, and riboflavin. The resins are insoluble in water, acids, or alkalies.

When a cation exchanger is ingested, the exchange process takes place in the gastrointestinal tract. Hydrogen or ammonium is liberated and sodium, potassium, calcium, magnesium, and other substances in the gastrointestinal contents are picked up. The liberated hydrogen and ammonium are absorbed, probably primarily as chlorides, and the resin, which remains unaltered except for the exchange process, passes through the gastrointestinal tract and is eliminated in the stool.

These resins can be utilized as a means of producing negative cationic balance by way of the stool. They may therefore be of value in conditions in which sodium[7], potassium[4], or other cations are retained abnormally, or in which an individual cation depletion state is desirable. Since the resins are not specifically selective of any one cation, to produce an individual deficiency it is necessary to feed back the other cations at a time when there will be a minimal amount of contact with the resin. It is our practice to give patients the resin at mealtime, and at bedtime the supplements of the cations which we do not wish to lose. The supplements consist of 2 gm. of potassium citrate, 2 gm. of calcium lactate, and a multiple vitamin capsule.

During the course of studying the reactions to these resins of laboratory animals, normal humans, and a series of patients with congestive heart failure, hepatic disease, and the nephrotic syndrome, we noted that large numbers of granular casts appeared in the urine. Quite frequently as many as 100 granular casts per low power field of a centrifuged specimen of urine have been found. The casts are associated with a trace of protein and a decrease in the pH of the urine. No blood cells have ever been observed in conjunction with these casts. The number of casts varies directly with the dose of the resin and inversely with the pH of the urine. The pH of the urine is dependent upon the amount of resin ingested, the larger doses resulting in more marked aciduria. When the pH of the urine is 5.5 or less, it is usual to find more than 30 to 40 casts per

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low power field. At a pH above 6 the casts are no longer present. The daily average dose of resin varies from 35 to 50 grams (3 to 4 tablespoons) divided into tablespoon doses and taken at mealtime. With this dose the pH of the urine is ordinarily 5.5 to 6, and the number of casts found is 20 to 30 per low power field.

The resin which we have been using almost exclusively is an ammoniated sulfonic acid exchanger (Permutit Z, Win 3000)[6]. In instances in which patients have been ingesting the resin for as long as 2½ years, the granular casts have been constantly present. Omitting the resin for 1 or 2 days results in the disappearance of the casts within a similar period of time. Within 24 hours after taking the resin again, the casts reappear. This sequence of events occurred when one of us ingested 45 gm. of the resin. Twelve hours later the urinary pH was 4.5. This was associated with slight proteinuria, and 60 to 70 granular casts were found in each low power microscopic field. Twelve hours after the resin was discontinued, the casts disappeared and the pH returned to 6. Patients who have been taking the exchange resin for prolonged periods have not shown any other clinical or laboratory evidence of renal insufficiency or damage which could be attributed to the resin. We have, however, observed episodes of elevated blood urea nitrogen and chloride with decreased carbon dioxide combining power in patients who were given large doses of the resin, or in whom there was pre-existing renal disease. Discontinuing or decreasing the dose of resin always resulted in a prompt return to normal levels.

The following cases are illustrative of the responses which we have obtained during the clinical use of the resins.

Case Reports. Case 1. P. E., a woman, 45 years of age, has chronic rheumatic heart disease, mitral stenosis, auricular fibrillation, and congestive heart failure. For 18 months prior to resin therapy, in addition to the usual treatment with digitalis and a low sodium diet, she was given mercurial injections twice weekly. For the past 2½ years she has been taking 35 to 50 gm. of the ammoniated resin almost daily at mealtimes, the cation and vitamin supplements being taken at bedtime. During this period she has continued to take digitalis but has not required any mercurial injections. She is ambulatory and eats the same diet as the rest of her family but she does not use a salt cellar. With this regimen her congestive heart failure is adequately controlled. She regulates the dose of resin herself, depending upon her daily weight as a guide.

During the entire period of 2½ years her urine has almost constantly contained granular casts. The number has varied from none to 50 per low power field, depending upon the dose of resin. When she discontinues the resin for a day or two, the casts disappear. Her blood chemical constituents, studied at intermittent intervals, have remained normal. There are no evidences of renal damage or insufficiency. During several brief trial periods the ammonium resin was omitted and ammonium chloride, a hydrogen sulfonic acid resin, and a hydrogen carboxylic acid resin were substituted. It was found that these substances also produced the granular casts but in smaller numbers than the ammonium resin. Because the diuretic response and effect upon the edema were not very marked, the hydrogen resins were not used for more than brief periods. The effect of larger doses for longer intervals is conjectural.

Case 2. S. B., a man, 37 years of age, had chronic rheumatic heart disease, mitral stenosis, auricular fibrillation, and severe congestive heart failure. His anasarca was intractable to routine therapy, including frequent injections of mercurial diuretics. He took the ammonium exchange resin intermittently for 16 months in doses ranging from 70 to 120 gm. daily, with good diuretic responses and control of his edema during these periods. Granular casts were found in his urine only when he took 120 to 140 gm. of the resin daily. At the time of his death, which was due to an attack of ventricular tachycardia, he had been taking 70 to 80 gm. of the resin daily for 4 weeks. Histological examination of his kidneys showed severe congestive changes. There were no abnormalities which could be attributed to the resin.

CASE 3. M. K., a male patient, aged 27, was hospitalized because of intractable ascites and massive hepatomegaly due to chronic rheumatic heart disease with trivalvular involvement. Because of lack of response to digitalis, a low sodium diet, and mercurial diuretics given 3 to 4 times weekly, it was decided to substitute resin therapy for the mercurial injections.

He was kept in bed for 3 weeks taking digitalis, a 200-mg. sodium chloride diet, fluids *ad libitum* (1500 to 2000 cc. daily), and mercurial injections 4 to 5 times weekly. Blood chemical analyses and renal function studies, including urea clearance and intravenous pyelography, were normal. His urine contained an occasional hyalin cast and no protein. During the first 2 weeks of the control period he lost 9 pounds, his weight decreasing from 165 to 156 pounds. His weight remained stationary for the third week and the ascites persisted. The mercurial injections were discontinued and 70 gm. of the ammoniated resin substituted. After 4 days, the dose was reduced to 35 gm. daily. During the first 9 days of resin therapy he lost 13 pounds. The ascites disappeared and the liver became smaller. At this time his diet was increased to contain 4 gm. of sodium chloride and he was permitted out of bed. His weight now remained at 143 to 145 pounds for 1 week. Increasing the dose of resin to 70 gm. resulted in a decrease in weight to 140 pounds. The dose of resin was then reduced to 50 gm. and he was discharged weighing 140 pounds.

On the third day of resin therapy, while he was taking 70 gm. daily, his urine had a pH of 5.5 and contained a trace of protein and 50 to 60 granular casts per low power field (centrifuged specimen). When the dose of resin was reduced, the casts and protein disappeared and the urinary pH rose to 6. For the next 7 days, while he was taking 35 gm. of the resin daily, no casts were present. When the dose was increased to 70 gm., the casts recurred and the pH of the urine again decreased.

During the course of resin therapy his blood urea nitrogen and creatinine remained normal, but there were several changes in the blood electrolytes and acid–base balance. While he was taking 70 gm. of the resin daily, the carbon dioxide–combining power decreased from 27 mM/L. to 21 mM/L. Reducing the dose of resin to 35 gm. daily resulted in an increase to 24 mM/L., but it fell to 18 mM/L. when the dose was again increased to 70 gm. daily. The chloride levels tended to vary inversely with the carbon dioxide combining power. Prior to the use of the resin the level of chloride was 95 mEq./L. With the 70-gm. dose, it increased to 111 mEq./L. and fell to 98 mEq./L. when the dose of resin was reduced to 35 gm. daily. Serum sodium, potassium, calcium, and phosphorus remained at normal levels during the course of resin therapy.

CASE 4. B. G., a woman, 66 years of age, suffered from hypertensive and arteriosclerotic cardiovascular disease and the nephrotic syndrome. For 2 years she had had massive edema of the lower extremities which was refractory to mercurial injections, grade 4 proteinuria, and hypoalbuminemia. She was anemic, her blood urea nitrogen was 56 mg. per 100 cc., and her uric acid 7.7 mg. Urine analyses showed a fixed specific gravity of 1010, proteinuria 4+, and numerous broad granular casts which were brown and yellow in color. There were 4 to 5 red and white blood corpuscles per high power field.

Upon admission to the hospital her weight was 165 pounds. Despite vigorous treatment with mercurial injections, a diet containing 200 mg. of sodium chloride, doubly concentrated plasma, and blood transfusions, her weight increased to 175 pounds. Her diet was now increased to one containing 4 gm. of sodium chloride, the mercurial injections were discontinued, and she was given 50 gm. of the ammoniated resin daily. In the next 10 days her weight decreased to 168 pounds but because of an elevation of the blood urea nitrogen and a decrease in the carbon dioxide–combining power, the resin was discontinued.

When first hospitalized, her blood chemical analyses were: urea nitrogen 60 mg. per 100 cc.; cholesterol 430 mg.; total protein 4.4 gm., albumin 2.5, globulin 1.9; calcium 3.3 mEq./L.; phosphorus 2.3 mEq./L.; sodium 132 mEq./L.; potassium 6.4 mEq./L.; carbon dioxide–combining power 21mM/L.; and chloride 90 mEq./L. Just prior to instituting resin therapy, the urea nitrogen was 20 mg. and the carbon dioxide–combining power was 29 mM/L., but after she had taken the resin for a 10-day period the urea nitrogen was found to be 66 mg., carbon dioxide–combining power 14 mM/L., sodium 130 mEq./L., potassium 4 mEq./L., and chloride 105 mEq./L. Urine analyses during the period of resin ingestion showed that in addition to the previously found broad, pigmented, granular casts, the granular casts which we have come to associate with resin therapy also appeared. The pH of her urine decreased from 6 to 5.2 When she stopped taking resin, the recently formed granular casts disappeared and the urinary pH increased to 6.2.

Discussion. All of the patients who were given the ammonium resin in sufficient amounts developed these urinary granular casts. To a lesser extent these casts were also found after the ingestion of the hydrogen resins, both sulfonic and carboxylic acid types[7]. Although these latter resins were not used for prolonged periods, our discussion may also be applicable to them because part of the ammonium resin is converted to the hydrogen form in the stomach. In the process of exchanging cations, the resin liberates ammonium ions which combine with the chloride ions of the intestinal contents. The ammonium chloride so formed is absorbed and the ammonium is converted to urea. The urea and the chloride, in the form of sodium chloride, are then excreted in the urine. This is associated with an increase in urinary volume and hydrogen ion concentration and a decrease in plasma alkaline reserve. The aciduria is the result of an increase in urinary titratable acid and ammonia. The increased urinary ammonia may be due in part to ammonium ions which had not been converted to urea or to the ammonia formed by the renal tubules. Simultaneously with the formation of ammonium chloride and the loss of sodium in the urine, the resin carries off sodium by way of the stool. In cases in which there is appreciable sodium retention, an increase in sodium is found in both the urine and stool. On the other hand, if the resin is ingested by patients or normal individuals who have no abnormal sodium retention, the amount of sodium in the stool is increased, depending upon the exchange process in the intestines, but the amount of sodium in the urine is decreased.

It is known that aciduria and increased urinary solutes, such as electrolytes and urea, are factors in cast formation[11]. We have found that the more intense the aciduria, whether as a result of large amounts of ingested ammonium chloride or the cation exchange resin, the greater the number of casts produced. It would seem, then, that in treated cases with marked sodium retention fewer casts should be found, at least until the sodium retention is overcome. This would explain the ease with which casts are produced in normal humans who ingested the resin. Another factor in the production of these casts might be a direct action of the absorbed ammonium upon the renal tubules. One hundred grams of the resin have an ultimate capacity of combining with 29 gm. of sodium as sodium chloride, and releasing enough ammonium to form 25 gm. of ammonium chloride. This ultimate exchange capacity is never reached *in vivo*, since an equilibrium is established at a much lower level between the resin and the cations of the intestinal contents. Nevertheless, large amounts of ammonium ions are released and converted to urea which is excreted and may therefore be of significance in the cast production.

There are then 3 possible factors in the mechanism of the formation of these casts, namely: the increase in the hydrogen ion concentration of the urine, the increased excretion of urea, and a possible irritative action of ammonium upon the renal tubules.

It is commonly accepted that the presence of numerous urinary casts signifies extensive renal irritation or damage and that the casts themselves, by blocking renal tubules, can cause further destruction of nephrons. However, it has been stated[11] that casts which form in the most distal parts of the nephrons, that is, the collecting tubules, are not retained but are washed out readily. Our findings in patients and rats who were fed the ammonium resin may fit into this category. Despite the cast formation,

we continued the use of the resins because of the excellent results obtained in patients with refractory edema. We soon found that by decreasing the dose, the advantages of the resin might still be obtained and few, if any, casts would form. All patients are instructed not to limit their fluid intake and to drink at least 1200 to 1500 cc. of water daily, in the hope that any casts which might tend to remain in the tubules would be washed out. In cases requiring larger amounts of resin, 50 to 100 gm. daily, the casts are constantly present, but no signs of renal insufficiency have developed.

Omission of the resin for 1 or 2 days is promptly followed by a disappearance of the casts. Patient No. 1 illustrates this response. Numerous casts have been present in her urine almost constantly for the 30 months that she has been taking the resin. Omitting the resin for several days always results in a return of normal urinary findings. Patient No. 2 had taken the resin intermittently for 16 months. For the 4-week period prior to his death, he took 70 to 80 gm. daily. Other than severe congestion, no unusual histological changes were demonstrable in his kidneys.

Nevertheless, ingestion of the resin may not be innocuous in instances in which there is pre-existing renal disease. Patient No. 4, with the nephrotic syndrome, in the 10-day period that she took the resin, developed urea retention and acidosis. It would seem, then, that normal or congested kidneys are able to cope with the changes brought about by ingesting the resin, whereas kidneys which are damaged may not.

Experimental Study. In a further attempt to see whether the ammonium resin affects the kidneys, a series of 12 rats was chosen for study. Three served as controls and the other 9 were divided into 3 groups. One group was fed 1 gm., the second group 3 gm., and the third group 5 gm. of the ammonium resin daily. Their diet consisted of rat pellets and oatmeal, the resin being mixed with the oatmeal. The doses of resin given to these 200 to 350-gm. rats were much greater, per unit of body weight, than those taken by humans. The group of rats receiving the bulky 5-gm. doses did not ingest the entire amount. Their average intake was 3 to 4 gm., which is 5 times the maximum and 10 times the average human dose that we have used. The rats were fed up to a period of 80 days.

Results. At regular intervals urine specimens were examined and found to contain granular casts. The specimens from the rats taking the larger doses of resin contained the greater number of casts. After periods of 30, 60, and 80 days groups of these rats were autopsied. Chemical analyses of heart blood of these animals including urea nitrogen, sodium, potassium, calcium, and chloride were normal. The kidneys of the rats which ingested the resin showed no histological abnormalities. They could not be distinguished from the kidney sections of the control animals.

Conclusions. 1. Cation exchange resins when ingested by normal humans, rats, or patients with edema produce granular casts in the urine. The number of casts varies directly with the dose of resin and inversely with the urinary pH.

2. Patients ingesting the ammonium exchange resin for prolonged periods of time (up to 30 months) have numerous casts in their urine but have not developed signs of renal insufficiency.

3. Rats fed the ammonium resin for periods up to 80 days developed casts in their urine. Histological examination of their kidneys showed no abnormalities.

4. The finding of urinary granular casts during the ingestion of a cation exchange resin is not an indication for discontinuing the use of the resin.

5. Cation exchange resins should be used cautiously, if at all, in patients with renal disease or insufficiency.

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OBSERVATIONS ON THE PLASMA POTASSIUM LEVEL OF MAN*

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Considerable interest in potassium metabolism and its relation to disease has become evident during the past few years. The development of the internal standard flame photometer[7], which affords a simple and accurate means of measuring the concentration of potassium in biological fluids, has probably played some role in this phenomenon.

The role of potassium in nerve and muscle physiology and in carbohydrate metabolism is well known. The effects on the plasma potassium level of hormones such as DOCA and ACTH and of such diseases as diabetes, renal failure, alkalosis, and familial periodic paralysis receive frequent consideration in clinical practice. Despite this, the mechanisms whereby many of the above factors influence the plasma potassium level are not certain. Indeed, disagreement still exists among certain textbooks as to the normal range of the plasma potassium level.

The purpose of the present paper is to consider several factors that are concerned with the level of potassium in the plasma and to report observations on arterial and venous plasma potassium levels that yield some information on the role of this ion in glucose metabolism. Inorganic phosphate is also considered in the latter problem.

Methods. The concentration of potassium in the plasma was measured on an internal standard flame photometer with an error of less than ±1%. However, because of the large amount of potassium in the erythrocytes as compared to the plasma, and because of the readiness with which the ion can diffuse out of the cells, strict attention to details in obtaining the plasma is essential. Blood was drawn in an oiled syringe and placed in a test tube containing dried heparin. The blood was then centrifuged immediately and the plasma drawn off within 15 minutes of removal from the blood stream. Inorganic phosphate in the plasma was measured by the method of Fiske and SubbaRow[27], and glucose by a modification[49] of the Folin method. Plasma for these determinations was obtained as described for potassium except that a small amount of sodium fluoride was added to prevent glycolysis.

In all instances where arteriovenous differences were calculated, both samples were obtained simultaneously. In 2 experiments hepatic vein samples were also obtained from a catheter passed through the right side of the heart.

For studies on the relation between potassium and carbohydrate metabolism, adequate priming doses of 50% glucose were

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administered intravenously in amounts calculated to raise the plasma glucose to between 500 and 800 mg. per 100 cc. This was followed by a sustaining infusion also containing glucose which was delivered by a constant infusion pump at such a rate that the plasma glucose level was maintained within a narrow range. Thirty minutes were allowed for equilibration between the start of the infusion and the obtaining of the first of 3 or 4 blood samples which were drawn at 10-minute intervals. In the insulin experiments, regular Lilly or Squibb preparations were used. Twenty units were given intravenously as a priming dose while 2 units per minute were delivered in the sustaining infusion, the glucose content of which was maintained at the previous level. Again, 30 minutes were allowed for equilibration before the start of collecting 3 blood samples at 10-minute intervals.

Glomerular filtration rate was estimated from the inulin clearance according to a standard technique[51].

Results. 1. Effect of Stasis on the Venous Plasma Potassium Level. Stasis induced by the application of a tourniquet for 2 minutes had no effect on the plasma potassium level (Table 1).

TABLE 1.—LACK OF EFFECT OF TOURNIQUET STASIS ON THE VENOUS PLASMA POTASSIUM LEVEL

Subject number	*Venous plasma potassium, mEq./L*	
	Control	*2 minute stasis*
1	4.0	4.0
2	4.0	4.0
3	4.2	4.1
4	4.2	4.2
5	4.4	4.2
6	4.7	4.5
7	4.7	4.5
Average	4.3	4.2

2. Normal Venous and Arterial Plasma Potassium Levels. Fasting venous plasma potassium levels were measured in 70 subjects without known electrolyte or metabolic disturbances, renal disease, or active infection. All were in reasonably good states of nutrition. The mean venous plasma potassium level in these subjects was 4.41 mEq./liter, $\sigma = 0.36$, range = 3.7 to 5.3. The level exceeded 5.0 mEq./liter in only 2 subjects.

Simultaneous arterial and venous blood samples were obtained in 57 subjects, not all of whom were "normal" according to the criteria given in the preceding paragraph. However, all patients were fasting and lying quietly in bed. On the average, venous plasma potassium exceeded arterial by 0.1 mEq./liter, an insignificant difference. The range of A-V plasma potassium differences was −0.9 to +0.5 mEq./liter. Arterial plasma potassium was equal to or greater than the venous plasma potassium in 29 subjects and was less than the venous level in 28.

3. Effect of Exercise on the Venous Plasma Potassium Level. Even slight exercise had an appreciable effect on the potassium content of plasma obtained from blood draining the exercised area. Twelve of the first 14 subjects recorded in Table 2 simply opened and closed their fists 10 times between the control and post-exercise samples. Such exercise is not infrequently used as an aid in obtaining blood samples from patients with difficult veins. The samples in these 12 subjects were taken from the cephalic vein and in each instance a noticeable increase in the plasma potassium level was observed. A similar effect occurred

when blood was obtained from the femoral vein after flexion of the lower leg every 2 seconds for 2 minutes (subjects 1 and 6, Table 2). However, when blood was obtained from a vein that did not drain the exercised muscles, no change in plasma potassium level was noted (subjects 15, 16, and 17, Table 2). Arterial blood was obtained in 6 subjects before and during exercise. No changes in arterial plasma potassium level were noted during exercise. The rise in plasma potassium level following exercise was transient, returning to the control value within 2 minutes in 6 of 8 subjects observed at this time.

TABLE 2.—EFFECT OF EXERCISE* ON VENOUS PLASMA POTASSIUM LEVEL

Subject number	Venous plasma potassium (mEq./liter) Control	At end of exercise	2 min. after exercise	Part exercised	Site of blood sample
1	3.7	4.5	4.2	Leg	Femoral vein
2	4.0	4.5		Hand	Cephalic "
3	4.0	5.3	4.0	"	" "
4	4.1	4.3		"	" "
5	4.1	4.5	4.1	"	" "
6	4.2	4.9	4.2	Leg	Femoral "
7	4.2	5.0		Hand	Cephalic "
8	4.3	4.9	4.6	"	" "
9	4.4	4.7	4.4	"	" "
10	4.5	5.8		"	" "
11	4.8	5.1		"	" "
12	4.8	5.2	4.4	"	" "
13	4.8	5.8		"	" "
14	5.2	5.5	5.1	"	" "
AVERAGE	4.3	5.0			
15	4.5	4.5		Thigh	Femoral vein
16	4.6	4.4		"	" "
17	5.2	5.2		Hand	Basilic "

* Exercise in the case of the hand consisted of opening and closing the fist 10 times, and in the case of the leg or thigh consisted of flexion every 2 seconds for 2 minutes.

4. EFFECT OF SEVERAL DISEASES ON VENOUS PLASMA POTASSIUM LEVEL. Fasting venous plasma potassium levels obtained in several diseases are recorded in Table 3. Although high plasma potassium levels have been reported among diabetic patients in acidosis[13,45] and low levels are not infrequent following insulin therapy[10,29,32,34,37,39,46], normal levels were observed in the 14 diabetic patients recorded in Table 3. These patients had been off insulin for 24 hours but were not in acidosis. Consistently low levels of plasma potassium were observed in 4 patients suffering from alkalosis, due to vomiting in 3 instances. This is in confirmation of previous reports[12,14,15,29,36,43]. Low plasma potassium levels were also characteristic of advanced hepatic failure.

High plasma potassium levels have been reported in renal disease[33,35,41,47,50]. A mean venous plasma potassium level of 4.9, σ=0.76 mEq./liter, was found in a group of 13 patients with early acute glomerulonephritis and 24 with chronic glomerulonephritis. Glomerular filtration rate was estimated by the inulin clearance in each of these patients and no more than 4 could be

classified as having terminal renal failure. The mean glomerular filtration rate for the group was 58 cc./min. (normal = 131 cc./min.). Nevertheless, 13 of the 37 patients had plasma potassium levels greater than the mean normal value plus 2 standard deviations. The plasma potassium levels are plotted in relation to the glomerular filtration rate in Fig. 1. The data plotted in Fig. 1 are composed of 70 separate experiments conducted in the 37 patients with glomerulonephritis. When more than one observation was made in a single patient, only the first was utilized in compiling the data in Table 3. A distinct tendency for the plasma potassium to rise above normal may be noted as the glomerular filtration rate falls below 60 cc./min. This is roughly 45% of normal and can hardly be classified as "terminal". However, considerable variation is noted in the plasma potassium level even when the filtration rate is very low. Vomiting and differences in potassium intake undoubtedly contribute to this variation. The lowest plasma potassium level recorded in Fig. 1 is from a patient with "potassium losing" nephritis[16].

In contrast to glomerulonephritis, normal plasma potassium levels were observed in congestive heart failure (Table 3). The mean glomerular filtration rate of this group, however, was 87 cc./min. Only 5 of the 24 patients had filtration rates below 60 cc./min., the approximate value at which the upward trend in plasma potassium level occurred among the nephritic patients. Several of these exhibited slightly elevated venous plasma potassium levels.

TABLE 3.—VENOUS PLASMA POTASSIUM LEVEL IN SEVERAL DISEASES

		Venous plasma potassium, mEq./liter		
Group	*Number of subjects*	*Mean*	*σ*	*Range*
Normal	70	4.4	0.36	3.7 to 5.3
Diabetes	14	4.6		3.3 to 5.3
Alkalosis	4	2.5		2.1 to 2.9
Hepatic failure	6	3.7		1.7 to 4.3
Nephritis	37	4.9	0.76	2.7 to 7.1
Congestive heart failure	24	4.5	0.44	3.6 to 5.8

5. Effect of Glucose and Insulin on Plasma Potassium and Inorganic Phosphate Levels. Administration of glucose reduces plasma potassium and inorganic phosphate levels in normal subjects[28,32] but has a lesser effect in diabetic patients[9,48]. Likewise, insulin reduces the plasma levels of both potassium and inorganic phosphate[10,32,34,37,39,53]. Data in confirmation of these earlier observations are recorded in Table 4. All determinations were done on plasma obtained from arterial blood. The normal subjects in Group 1 received 100 gm. glucose by mouth, while those in Group 2 were given glucose by means of a constant intravenous infusion so as to maintain reasonably stable plasma glucose levels. Although considerably higher plasma glucose levels were achieved and maintained in the patients given glucose intravenously, the decline in plasma potassium was comparable for both groups. Decreased arterial plasma potassium after glucose administration was observed in all subjects of both groups. Similarly, inorganic phosphate decreased in every normal subject.

Among the diabetic patients, intravenous glucose caused no change in the arterial plasma potassium level. However, inorganic phosphate did decrease. Although this decrease was slight it occurred in every patient. Insulin, administered to 10 of the diabetics in the glucose infusion, caused a considerable decrease in both potassium and inorganic phosphate levels in the plasma.

6. Effect of Glucose and of Insulin on Arterio-Venous Plasma Potassium and Inorganic Phosphate Differences. The effect of glucose infusion and of insulin added to the glucose infusion on the arterial and venous plasma levels of potassium and inorganic phosphate in 6 diabetic and 4 normal subjects is summarized in Table 5. During the control periods in the diabetics the plasma levels of potassium and inorganic phosphate exhibited very little arterio-venous difference. Although the average arterial plasma glucose level was 238 mg., the arterio-venous difference was only 4 mg.

The effect of glucose on the arterial and venous plasma levels of potassium and inorganic phosphate was studied in 8 normal subjects. Four of these were given glucose by constant intravenous infusion while a single oral dose of glucose was given to the other 4 subjects. The data for the 2 groups were similar so they were averaged and presented in Table 5. The effects of glucose on potassium and inorganic phosphate in the normal subjects were similar to those in the diabetic patients, except that the normals exhibited greater decreases in arterial plasma potassium and inorganic phosphate levels than did the diabetics. Venous plasma potassium did not decrease during glucose load and exceeded the arterial level in every patient. Insulin was studied in only 1 normal subject. It decreased the plasma levels of potassium and inorganic phosphate in both arterial and venous plasma, but again, venous plasma contained more postassium than did arterial plasma.

During the infusion of glucose the mean arterial plasma glucose level rose to 567 mg. per 100 cc. in the diabetics. The arterio-venous difference was only 21 mg. compared to 39 mg. in 8 normal subjects who had somewhat lower plas-

TABLE 4.—EFFECT OF GLUCOSE AND OF INSULIN ON ARTERIAL PLASMA GLUCOSE, POTASSIUM, AND INORGANIC PHOSPHATE LEVELS*

Group	*Number of subjects*	*Procedure*	*Mean arterial plasma level*		
			Glucose (mg./100 cc.)	*Potassium (mEq./L)*	*Inorganic phosphates (mg./100 cc.)*
Normal	10	Control	88	4.6	3.1
		Oral glucose	204	4.2	2.2
		Δ	+116	−0.4	−0.9
Normal	10	Control	88	4.3	3.5
		Glucose infusion	482	3.9	3.0
		Δ	+394	−0.4	−0.5
Diabetic	14	Control	228	4.6	3.2
		Glucose infusion	549	4.7	2.9
		Δ	+321	+0.1	−0.3
Diabetic	10	Glucose infusion	593	4.7	3.0
		Glucose + Insulin	555	3.7	2.0
		Δ	−38	−1.0	−1.0

* Two or 3 consecutive samples were averaged for each subject except in the case of the normal subjects given oral glucose. In these instances samples from the period of highest plasma glucose level were utilized.

ma glucose levels. The glucose infusion had no effect on the arterial plasma potassium level, but the venous plasma contained more potassium than did the arterial plasma in each patient. The addition of insulin to the glucose infusion resulted in a considerable decrease in plasma potassium in each patient. Despite this, the potassium level of the venous plasma continued to exceed the level of the arterial plasma. Inorganic phosphate plasma levels decreased slightly during glucose infusion and considerably when insulin was added to the infusion. However, arterio-venous differences did not develop.

The effect of glucose on the hepatic venous plasma content of potassium and inorganic phosphate was studied in 1 normal and in 1 diabetic subject. The effect of insulin added to the glucose infusion was also observed in the normal subject. Glucose caused a greater fall of potassium content in hepatic venous plasma than in either arterial or peripheral venous plasma in both patients. In the diabetic patient the hepatic venous plasma contained considerably less potassium than did the arterial plasma during the glucose infusion. However, inorganic phosphate decreased proportionately in each of the 3 sites in both patients.

Serum sodium, plasma chloride, whole blood sodium, and potassium and hematocrit were also measured. All these measurements showed slight decreases during the infusion of glucose, but there were no significant differences between the simultaneous samples from the 3 sites.

TABLE 5. EFFECT OF GLUCOSE AND OF INSULIN ON ARTERIAL AND VENOUS PLASMA LEVELS OF GLUCOSE, POTASSIUM AND INORGANIC PHOSPHATE IN NORMAL AND DIABETIC SUBJECTS*

Group	*Substance measured*	*Source of plasma*	*Mean plasma level during*		
			Control periods	*Glucose infusion*	*Glucose + Insulin*
8 Normals	Glucose, mg./100 cc.	Artery	91	397	
		Vein	88	358	
		A–V	3	39	
	Potassium, mEq./L.	Artery	4.3	4.0	
		Vein	4.6	4.6	
		A–V	−0.3	−0.6	
	Inorganic phosphate, mg./100 cc.	Artery	3.2	2.2	
		Vein	2.8	2.3	
		A–V	0.5	−0.1	
6 Diabetics	Glucose, mg./100 cc.	Artery	238	567	539
		Vein	234	546	523
		A–V	4	21	16
	Potassium, mEq./L.	Artery	4.7	4.6	3.8
		Vein	4.8	5.0	4.2
		A–V	−0.1	−0.4	−0.4
	Inorganic phosphate, mg./100 cc.	Artery	2.9	2.5	1.8
		Vein	2.8	2.6	1.8
		A–V	0.1	−0.1	0.0

* Four of the 8 normal subjects received glucose by mouth and 4 by vein. Each datum represents the average of 2 or 3 periods except in those given oral glucose where period of maximum plasma glucose level was utilized.

Discussion. Red blood cells contain much more potassium than does the plasma. Since potassium can diffuse out of cells so readily under certain circumstances, strict attention to details in obtaining plasma is essential if measurements of plasma potassium level are to be valid. Minimum trauma to

the blood cells and rapid separation of the plasma from the erythrocytes are important. Venous stasis does not affect the plasma potassium level, but exercise of muscles drained by the vein used for sampling must be avoided. When all precautions are observed, the fasting venous plasma potassium level is usually between 4 and 5 mEq./liter with a mean value of 4.4 mEq./liter. Levels above 5 mEq./liter are very rare.

The plasma potassium level may be increased or decreased in disease. Low levels are characteristic of the attack of familial periodic paralysis[1,3,8,25,30,52], severe hepatic failure, alkalosis[12,14,15,17,36,43,54] (especially when due to vomiting), and following insulin therapy of diabetic acidosis[13,29,34,45,46]. Nephritis may be associated with low plasma potassium levels[2,11,16] or, more commonly, with high levels[26,33,35,41,47,50]. Levels sufficiently high to produce adverse cardiac effects[26,35,41,47] are among the most serious complications of acute renal shutdown and advanced renal failure due to any cause. The data presented in Fig. 1, however, indicate that the plasma potassium level may rise well before the terminal stage of nephritis is reached. Whether the moderate increases in plasma potassium recorded in Fig. 1 are the result of diminished renal excretion or of shifts of potassium between extracellular and intracellular phases is not certain.

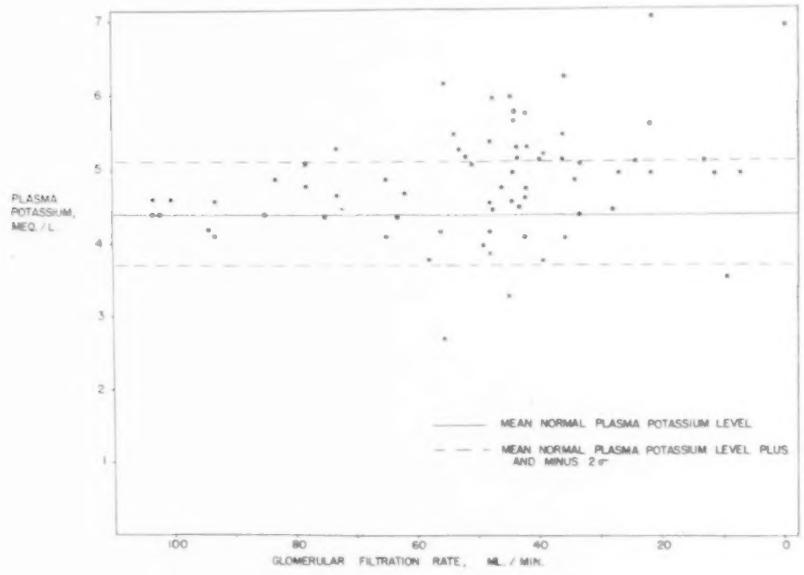

FIG. 1.—Relation between glomerular filtration rate and venous plasma potassium level. 70 experiments in 37 patients with glomerulonephritis.

Activity of a muscle has been known to cause loss of potassium from the muscle[19,23]. These observations, however, have been made after considerable exercise[20,24,38] or after direct stimulation of muscles[4,21]. The increase in potassium content of only mildly exercised muscle in man is, therefore, striking. Other observers have noted similar[31] or even opposite[48] effects in muscles exercised when their blood supply is decreased by application of pressure cuffs.

However, many patients with nephritis are able to excrete a considerably greater than normal proportion of their filtered potassium. At times potassium excreted in the urine may exceed the amount filtered[6,16,40], a fact that can be explained only by an ability of the renal tubule cells to excrete potassium[5,6,44]. This phenomenon can be so marked that certain patients with moderately severe renal disease may be said to suffer from "potassium losing" nephritis[2,11,16]. In any case, the phenomenon of increased per cent excretion of filtered potassium probably militates against accumulation of potassium in extracellular fluid in patients with advanced renal disease whose filtered loads of potassium may be considerably reduced. It might be noted in this relation that reasonably normal plasma potassium levels were noted in 24 patients with congestive heart failure, a condition also associated with decreased glomerular filtration rate. Five of the heart failure patients had filtration rates below 60 cc./mn., the point at which plasma potassium began to increase among the nephritic patients.

The remainder of the data presented in this paper were concerned with the behavior of potassium and inorganic phosphate in arterial and venous plasma as influenced by glucose loading and by insulin. A decrease in plasma potassium and inorganic phosphate occurs during glucose loading[3,26,32]. Little or no decrease in these substances has been reported in diabetic patients under similar circumstances[9,42]. The data presented in Table 4 confirm these observations, with the exception that inorganic phosphate did decrease slightly during glucose loading in the diabetics. Insulin administration has been found to decrease plasma potassium and inorganic phosphate levels[19,32,34,37,39,53]. This is also confirmed in Table 4. The decreases in plasma potassium and inorganic phosphate levels during glucose infusions and after insulin administration were not due to increased urinary excretion. Rather, potassium and inorganic excretion rates fell to very low levels, especially during insulin[9,18,42].

Because of observations of this type, potassium and inorganic phosphate have been assumed to penetrate into cells both during the utilization of carbohydrate by the cells and along with the deposition of glycogen in the liver. The arterio-venous differences for plasma potassium during glucose loads recorded in Table 5 indicate that in man potassium actually leaves the peripheral tissues during glucose loading in both normal and diabetic subjects. Despite the considerable fall in arterial plasma potassium after insulin, the negative arterio-venous difference for potassium persisted. This suggests that potassium was probably being localized in certain organs at a rapid rate and that, in an effort to maintain the plasma level, potassium is contributed by the peripheral tissues. Deposition of potassium along with glycogen in rat liver has been demonstrated in experimental animals[22]. Preliminary observations on the potassium content of arterial, peripheral, and hepatic venous plasma suggest that potassium is localized in the liver of man as well during glucose loading and after insulin administration. Localization in other organs may also occur under these circumstances.

Although the arterial plasma inorganic phosphate behaved as did potassium during glucose loading and insulin administration, arterio-venous differences did not develop. Inorganic phosphate and potassium, therefore, appear to behave differently in response both to glucose load and to insulin.

Summary. 1. The fasting venous plasma potassium level in 70 normal

subjects was 4.4 mEq./liter, $\sigma = 0.36$, range = 3.7 to 5.3 mEq./liter.

2. The venous plasma potassium level was not affected by stasis, but was increased transiently by even slight exercise in veins draining the exercising muscles.

3. Under fasting conditions arterial and venous plasma contained the same amount of potassium with but rare exception.

4. Plasma potassium levels were low in alkalosis and advanced hepatic failure, normal in diabetics not in acidosis and in congestive heart failure, and frequently increased in patients with renal disease whose glomerular filtration rates were less than half of normal.

5. Plasma potassium level was reduced by glucose loading in normal but not in diabetic subjects. Insulin reduced plasma potassium in all subjects. Inorganic phosphate behaved in a similar fashion except that it did decrease slightly in the diabetics during glucose loading.

6. Venous plasma contained more potassium than did arterial plasma during glucose loading and insulin administration and despite falling arterial plasma potassium levels. Differences did not develop in inorganic phosphate levels of arterio-venous plasma.

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THE EFFECT OF AUREOMYCIN ON VENOUS CLOTTING TIME

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Conflicting reports have appeared concerning the effect of antibiotics on coagulability of the blood. Moldavsky, Hasselbrook and Cateno[5]; Macht[3]; and Macht and Farkas[4] have presented evidence to suggest increased coagulability in animals and human subjects following administration of penicillin, streptomycin and aureomycin. Harned and coworkers[1] found no such effect when aureomycin was administered to dogs. Ross and coworkers[6] observed no change in blood coagulability in human subjects when aureomycin was administered orally. The question is potentially a serious one, should the weight of evidence favor those workers who found a decrease in the venous clotting time due to the administration of an antibiotic. The implication in regard to thromboembolic disease has been discussed[2]. The following study was undertaken to extend the observations already made.

Material and Method. The effect of aureomycin on venous clotting time in human subjects has been studied by a modification of the Lee-White method of determining coagu-

TABLE 1.—VENOUS CLOTTING TIMES (MINUTES) IN 11 NORMAL MALE SUBJECTS.

subject / day		WF°	WB°	BW°	RC°	RF°	HP°	RH°	JG°	CC°	BB°	LG°
control	1	14.0	23.0	24.5	11.0	13.5	10.5	9.5	8.5	9.5	12.5	15.5
	2	8.5	20.0	18.5	7.0	10.0	10.0	16.0	13.5	8.5	10.0	10.5
	3	13.0	16.0	13.0	9.5	10.5	11.0	13.5	10.0	9.0	20.0	16.0
	4	12.0	17.0	16.5	X	12.0	11.5	14.0	9.0	13.5	14.0	15.5
	5	17.0	14.5	15.0	11.0	12.5	12.0	8.5	13.0	12.5	18.0	13.5
aureomycin 1 or 2 gm followed by 500 mgm every 6 hours	2 hr	12.0	16.5	15.0	13.0	14.0	15.0	11.0	11.0	11.0	15.0	13.5
	4 hr	15.5	15.5	15.0	9.5	16.0	11.5	10.5	12.5	14.5	15.5	15.5
	6 hr	15.5	17.0	13.0	11.5	16.5	11.0	11.5	10.5	13.5	15.0	12.5
	6	19.0	17.0	14.0	11.0	16.0	19.0	12.5	15.0	16.5	13.0	11.5
	7	14.0	12.0	14.5	16.5	13.0	16.0	14.5	13.5	14.0	15.5	16.0
	8	18.0	16.0	15.0	15.5	13.0	14.0	13.0	12.0	13.5	13.0	13.0
	9	17.5	19.0	X	14.5	13.5	13.0	14.0	18.0	13.0	X	X
control	10	11.5	17.0	14.0	15.0	15.0	21.0	16.0	12.5	15.0	16.0	15.0
	11	12.0	17.5	16.5	13.5	15.5	12.5	14.0	8.0	13.0	12.5	14.0

X = data missing
° = 5 tube method
° = 3 tube method

lation time. A clean vena puncture was made using a 20-cc. syringe and 1 cc. of blood was placed in each of three 10 mm. by 75 mm. glass tubes. All glassware used was carefully cleaned with a soap-detergent mixture, rinsed several times with distilled water and oven-dried. Syringe and tubes were rinsed with normal saline just prior to being used. If the vein was not pierced cleanly on the first attempt, a new site was approached with new equipment. The tubes were then allowed to stand for 3 minutes without manipulation. Following this period 1 tube was tilted toward the horizontal at half-minute intervals until no change in the surface of the blood occurred when the tube was held in a horizontal position. The second tube was then treated in a similar way, as was the third tube, if still unclotted. A stopwatch was started when blood entered the syringe and was stopped when

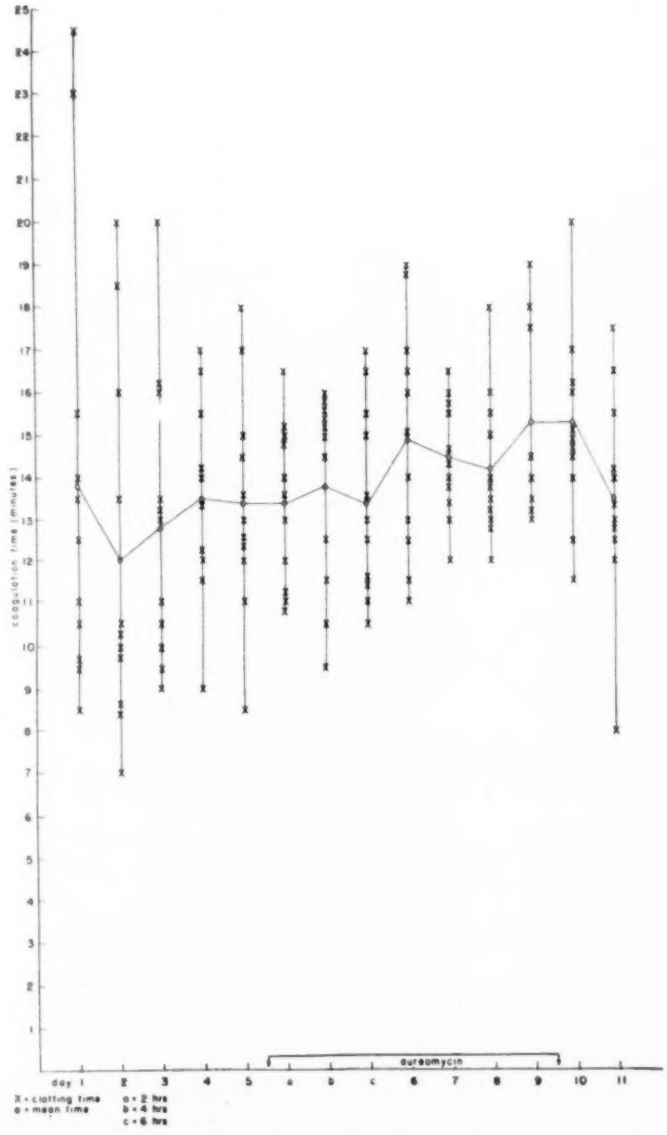

FIG. 1.—Observed values, range and means of coagulation times.

clotting occurred in the last tube. The time was taken to the nearest half minute. All coagulation times were done by the same person (WAB).

The following experiment was carried out on 11 healthy adult males. Daily coagulation times were performed each morning for 5 successive days. At the end of this period a single oral dose of aureomycin was given; 1.0 gm. to 4 subjects and 2.0 gm. to 7 subjects. Coagulation times were then performed at 2, 4 and 6 hours. Following this, aureomycin was administered to all subjects in doses of 500 mg. every 6 hours for a total of 5 days. In 3 instances the drug was stopped after 4 days because of gastrointestinal toxicity. Coagulation times were performed daily during this period. After allowing 24 hours for drug excretion, 2 final control observations were made on successive days.

The method was modified further in some instances in an effort to bring control values within a closer range. In 7 instances, 5 tubes were used instead of 3, and in 5 of these the tubes were kept in a constant temperature water bath at 25° C. to nullify possible effects of changes in room temperature. In each individual studied the method was the same throughout the experiment. No significant difference was noted between 3-tube, 5-tube, room-temperature or water-bath methods of observing coagulation times.

Results. Table 1 shows values for clotting times obtained on each subject. Fig. 1 indicates the daily values, range and mean of coagulation times done on the 11 subjects during the initial control period, acute and chronic phases of the test period and final control period. It is evident that no fall in mean coagulation time occurs during the test period. It is also demonstrated that the range of observations during the test period remained within the range of those made during the control period.

A slight rise of mean coagulation time during the test period appears to be the trend but statistical analysis shows the major rises and falls of the curve to be not significant.

Comment. Control observations show such a range of values that changes must be marked and persistent before their significance is obvious. The significance of minimal changes can only be determined after a great number of observations. Testing of venous clotting time is an artificial technique carried out under unphysiologic conditions at best. The great number of variable physical factors which may produce minor alterations in coagulation time makes rigid control impossible. It is a convenient method of determining a decrease in coagulability of the blood when there is such a gross prolongation of the clotting time as to allow no doubt as to its significance: for example, 30 minutes or more by this method. The significance of a shortening of coagulation time would be difficult to establish since most errors in technique tend to decrease the coagulation time.

Conclusion. Aureomycin produces no significant alteration of the coagulability of the blood in normal human subjects as measured by a modification of the Lee-White method.

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RECENT TRENDS IN BREAST FEEDING: A REVIEW

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ONE of the most striking things that emerge from a review of recent literature on breast feeding is the difference between European and American attitudes toward the clinical importance of this natural function. Thus an American author[7] notes without critical comment that 23% of the infants born in hospitals in the northeastern part of the United States are entirely breast-fed, whereas a European author[45] shows considerable concern about a hospital in which a mere 50% of the babies are entirely breast-fed. In recent years numerous articles[11,22,37-39,44,61,65,70,76,80,92] have been published in Europe on the problem of preparing, preserving, and distributing human milk for the benefit of babies for whom direct breast feeding is not otherwise available. No articles dealing with such problems are to be found in American medical literature of the same period.

Work in this field may be conveniently divided into 1) breast feeding versus formula feeding of the newborn; 2) the physiological factors affecting breast-feeding; and 3) the sociological and psychological factors affecting breast feeding.

Breast Feeding Versus Formula Feeding of the Newborn. Studies indicate that breast-fed babies generally

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are subject to a lower risk of morbidity and mortality than those who are reared upon formula feeds. However, the degree of risk varies tremendously with differences in the environment or culture in which the studies are made. Thus, when an attempt was made to introduce formula feeding of infants among village peoples of southern Egypt[86], almost every baby died despite the fact that vitamin supplements were furnished and a presumably suitable feeding mixture was formulated. In Switzerland[9] the morbidity rates for artificially fed babies are reported to be twice those of the breast-fed. In the United States[85] formula-fed infants develop a significantly higher number of respiratory infections than do those who have been breast-fed for 3 or more months. A comparable vulnerability to other less common infections is not demonstrable. The opinion of earlier writers that artificially-fed babies lack alertness is given some support by the experimentally controlled observations of Davis *et al.*[17], who have shown that breast-fed infants show slightly but significantly more general body activity after the sixth day of life than do those who are artificially fed. The body composition of the breast-fed baby is reported to differ from that of the artificially-fed baby[35].

For the feeding of *premature infants* most authorities are agreed that breast milk has special advantages. This view is again upheld by Ford[25], who from a study of 86 premature infants finds that those who are fed breast milk fare better, while beyond that age there is little difference between the breast-fed and artificially-fed infants. Aldrich[4] emphasizes that supplementary foodstuffs may be necessary for very small premature infants. Schreier[79] has reported that the addition of protein hydrolysates to breast milk appears to enhance the retention of nitrogen by premature infants. The importance of nursing premature babies at the breast after they leave the hospital is emphasized by Moller[46]. He readmits mothers to the hospital just before the babies are due to leave in order to teach the latter to suck the breast.

Whether *erythroblastotic* infants should be breast-fed by their mothers is a question that appears to be unsettled at the present time. Cathie[13] favors such feeding after finding that, although Rh antibodies may be excreted in the milk, they are not absorbed from the infant's gastrointestinal tract. Amato[5] takes the same point of view, but on the grounds that these antibodies are rarely excreted in the milk. Zischka and Winkler[99] report a case in which a breast-fed erythroblastotic infant developed a late anemia which was relieved by boiling the breast milk. A somewhat similar case is reported by Desbuquois[18].

Whether *carcinogenic factors* are present in human milk is an important and intriguing question. The transmission of mammary cancer in mice via a milk factor has been discussed by Berner[10] and Gross[27]. There is as yet no clear evidence that the same phenomenon occurs in the human. There is further evidence that mammary cancer occurs more frequently among the relatives of women having such tumors than among the general population[40,59]. Gross *et al.*[28], moreover, using the electron microscope, find suggestive particles in the breast milk of women with a family history of mammary cancer. On the other hand mammary cancer is found among women who have not themselves been breast-fed[34]. Furthermore, if a carcinogenic agent is transmissible from mother to daughter through the breast milk, then mammary cancer should be more common among the maternal relatives of patients with mammary cancer than among the paternal relatives. This has

not been found to be true in 2 small series[40,59]. In addition there has been recent confirmation[16] of the earlier work of Adair[3] that more women afflicted with mammary cancer give a history of no lactation or disordered lactation than do healthy controls.

With respect to the *comparative composition of human and cow's milk*, little new information has been added recently to previously accumulated knowledge. Excellent reviews of available data have been provided by Stone Bakwin[88] and by Platt and Moncrieff[64]. Lately, Catteneo and Maggiora-Vergano[14] have found that lysozyme is present in human milk and colostrum but not in cow's or sheep's milk. They consider the presence of this substance to be of great importance for the development of proper flora in the infant's gastrointestinal tract. Hildebrandt[33] has called attention to some differences in the vitamin content of human and cow's milk.

Extreme statements about the *psychological advantages of breast feeding for the infant* have recently come under critical review. Orlansky[56] in an extensive review of anthropological and psychological literature concludes that there is little evidence for the belief that the care which an infant receives, including breast feeding, influences the development of its adult personality. Newton[52] states that, although most workers have observed some sort of relationship between early feeding experience and later behavior, the nature of the relationship is such that, in general, it does not suggest cause and effect. Other factors, such as mothers' attitudes, may affect both the feeding experience and the later behavior of the child, and thus indirectly explain this relationship. Stone and Bakwin[88] believe that breast feeding is an important step in establishing interrelationships between mother and baby and in meeting the baby's emotional needs. However, they caution that the virtues of breast feeding should not be stressed to such a degree that the mother who fails to nurse will feel a sense of guilt. Aldrich[4] states that although breast feeding is probably the best method of providing babies with a sense of security, concrete proof is needed to support any claim that it provides psychological values of crucial importance for the infant's proper development.

The importance of breast feeding for the satisfaction of *maternal emotions* is emphasized by Trainham and Montgomery[90], MacNeil[41], and Aldrich[4]. A remarkable case report by Blickenstorfer[12] suggests that both lactation and "maternal behavior" in the human are dependent upon the action of the pituitary lactogenic hormone. If this be correct, it is consistent with observations made some years ago on virgin rats by Riddle *et al.*[69], in which "maternal behavior" was induced by administration of prolactin.

Physiological Factors Affecting Breast Feeding. Studies of the basic physiology of *milk secretion* continue to be made, but mainly in experimental animals. Recent reviews of this work have been provided by Folley[24], Petersen[62], and Saner[77].

The expulsion of milk from the breast or *"let-down reflex"* has recently been investigated in the human female. This phenomenon, first clearly recognized in dairy cows by Ely and Petersen[21], is a process entirely distinct from the secretion of milk and is best described as an active ejection of milk from the breast in response to the stimulation of the teat or nipple by sucking or milking manipulations. It is a reflex mechanism in which afferent nervous impulses from the nipple are carried to the posterior pituitary gland which then releases its oxytocic principle. This substance reaches the breast by the blood stream

and there acts on contractile cells surrounding the alveoli. Thus the contents of the alveoli are forced into the larger ducts where they are more easily available to the nursling or to the milking machine. The earlier work on this phenomenon in cows by Ely and Petersen[21] and Petersen and Ludwick[63] has been confirmed in the same animals by Peeters *et al.*[57,58]. The problem of the presence and function of contractile elements around the alveoli has been summarized by K. C. Richardson[67]. The same author has also demonstrated the presence of myoepithelial cells in the goat's mamma[68].

Waller[93] and Newton and Newton[49] have demonstrated that the reflex is operative in lactating women. Its action there is recognizable in the well-known "drooling" or spurting of milk from the nipple of the breast opposite to that from which the baby is sucking. In addition it accounts for the commonly observed uterine cramps which accompany suckling of the infant at the breast. These and other symptoms and signs suggestive of adequate function of the let-down reflex have been shown by Newton and Newton[54] to occur more frequently in successful than in unsuccessful breast feeders. These authors have also demonstrated that the reflex can be duplicated by the injection of Pitocin, and this technique has been used by them[51] and by Gunther and Stanier[31] to empty the breasts of milk. Another important feature of this reflex is that it can be set in motion or inhibited by emotional or psychological factors. Thus anticipation of the baby coming to feed may start it, while fear, pain, or embarrassment may inhibit it[49]. The importance of the oxytocic principle of the posterior pituitary in this reflex suggests the possibility that this hormone may be primarily concerned with action on the breast and only secondarily with action on the uterus.

Evidence continues to accumulate that *sucking stimulation* is of paramount importance in establishing and maintaining an adequate milk supply.

Lactation induced by sucking stimulation alone, without preceding pregnancy, has long been noted in occasional physiological, anthropological, and historical records[55]. Sarbu[78] has recently offered an interesting example of this by reporting that a woman who had not been pregnant for 20 years began to secrete milk from her right breast as a result of offering it to her infant grandchild to pacify him. Secretion commenced in 8 days and for a period of 2 months was the sole nourishment of the infant. Another type of evidence comes from the recent fashion of self-demand feeding. The baby who is on such a plan usually goes through a period of demanding more sucking than the schedule baby is allowed[53,81]. This may explain the belief that breast feeding may be more easily established under a self-demand rooming-in plan of infant care[23]. Manual expression of milk is a technique which gives artificial sucking stimulation. The importance of such manual expression has been recently reemphasized by Waller[96] and F. H. Richardson[66]. Sucking stimulation is often artificially limited by the use of schedules for feeding, by limitations on the duration of each feeding, and by banning the use of both breasts at each feeding. Sucking stimulation may be reduced by the use of bottles. Experimental observations by Davis *et al.*[17] indicate that cup- and bottle-fed infants soon develop a weaker sucking reflex than those who are breast-fed. Ungar[91], after a careful study of 884 infants, finds that the duration of breast feeding is doubled when supplemental feedings are administered by spoon instead of by bottle. He recommends semi-liquid precooked cereal to be offered before each breast feeding. De Ritis[20] suggests supplemen-

tation through the use of spoon feedings of milk concentrates in the middle of breast feedings.

Various substances or devices have been used recently in attempts to find efficient *lactagogues or lactagogic routines*. These studies are difficult and modern statistical methods have not in general been employed. Agents which have recently been investigated with some reported success include thyroid substance and thyroxine[73], anterior pituitary extract[72], Lugol's solution[71], iodinated casein[74], Fenugreek oil[89] and breast-milk enemas[8]. It has been suggested that the traditional virtues of beer and stout as lactagogues derive from the liberating action which any alcoholic beverage may be expected to exert upon emotional inhibitions of the let-down reflex[49]. Several European reports suggest that exposure of the breasts to radiant energy may have a lactagogic effect. Gergely[26] claims good results with the use of short-wave therapy, though admitting that associated psychological factors may also play a role. De Feo[19] also reports good results with the use of ultrashort waves, as does Zangri[98] using ultraviolet rays. Waller[94,95] emphasizes the beneficial effects of an elaborate routine which includes prepartal massage of the nipples and expression of colostrum and milk. He finds that 83% of the women who have been taught to express their colostrum for the last 3 months of pregnancy continue to breast-feed at the end of 6 months. Only 42% of the control cases do so. In a later series he shows that 79% of 300 primiparae who went through his routine still breast-fed their infants after 6 months.

Certain common *disorders* and *complications* of the breasts, nipples, and lactational function are of interest in the light of the newer physiologic data noted above. Postpartum engorgement of the breast is a very common and painful condition, and yet it has received comparatively little attention from investigators. Naish[48] is of the opinion that the engorged breasts (at any rate at the beginning) are overfull, not of milk, but of blood. Waller[94], however, attributes engorgement to inadequate emptying of the breast. He shows that of women who were instructed to empty their breasts by hand before and in the first few days after delivery, only 25% developed severe engorgement compared with 56% of those who did not. Newton and Newton[51], using Pitocin to cause artificial let-down, show that the degree of engorgement increases with the amount of milk in the breast. They postulate that engorgement begins with the retention of milk in the alveoli. The distended alveoli then compress surrounding milk ducts. This reduces the outflow of milk and may lead to secondary lymphatic and venous stasis. Important causes of the primary retention of milk in the alveoli may be failure of the let-down reflex, reluctance of the mother to allow enough sucking stimulation, and hospital routines which do not allow enough time for adequate emptying. Nipple pain and nipple fissures are common occurrences during early lactation. Gunther[30] notes that characteristic lesions of the nipple occur if the baby sucks for prolonged periods without getting milk. Various methods have been used in the past for the prevention and treatment of nipple pain and fissures. Abramson[2] and McKenzie[43] use careful breast cleansing and plastic nipple shields in large series of women with considerable success. Preliminary investigations on different substances used on the nipples show that washing with soap may be injurious, while hydrous lanoline and White's A & D ointment may be helpful in reducing pain and the development of fissures[53].

Mastitis and breast abscess are the most serious complications of lactation. Leary[36], combining several series of figures, including his own, finds an incidence of mastitis of 2.1%; of these 27%, or approximately 0.5% of all postpartum women, developed a breast abscess. The advantages of penicillin in treating these infections has been shown by Newton and Newton[50]. These authors also emphasize that failure of the let-down reflex from one cause or another may lead to stasis of milk in the breast and predispose to the entrance of infection. In general, American authors have not recommended continuing lactation during a breast infection; however, this has been done with success in England by Walsh[97].

Sociological and Psychological Factors Affecting Breast Feeding. Recently there has been considerable interest in the sociological, environmental, and physical influences related to breast feeding. Söderling[82] finds that full-time employment away from home is definitely destructive to lactation, even though the mother is expected to do no housework. Waller[95] in a study of 400 English women finds that multiparae and younger women have more milk in the early days of lactation than the primiparae and older women. Herlitz's[32] study on 4084 Swedish women shows that older women nurse their babies longer but feed them exclusively by breast for a shorter time. Multiparae nurse more than primiparae, but sex and birth weight of the child, if above 2500 grams, do not seem to influence nursing. Children of unmarried mothers are breast-fed only slightly less than children of married mothers in the Swedish study. An extensive English study indicates that the incidence of breast feeding is about the same for all social classes[15]. Mildly deficient diets do not appear to be related to lactation success. In fact, in a study of 5000 English women[60] it is noted that the young primiparae given dietary supplements are *less* apt to breast feed than the control group. Older women and multiparae lactate just as much in the control group as in the group receiving dietary supplementation. However, the extremely deficient diets the German women received after World War II did have a definitely deleterious effect on the composition of their milk[47,84]. Many other environmental and physical factors continue to be reported to influence the composition of milk[42]. One new type of variation has been recently noted by Gunther and Stanier[31] who observe a diurnal variation in fat content. They report that breast milk has less fat during the night. This may help explain the fact that self-demand breast-fed infants appear to desire more feeding during the night[53].

The custom of breast feeding varies tremendously from region to region and nation to nation. In a recent analysis of the reports of 2,513 hospitals distributed throughout the United States Bain[7] finds that 38% of the babies are totally breast-fed at the time of discharge from the hospital and 35% are totally bottle-fed. However, decided regional variations appear. For instance, 61% of the babies in the northeast are discharged totally bottle-fed as opposed to 18% in the southeast. Although the incidence of absolute breast feeding in Britain seems to be higher, similar regional variations occur. In a study[15] of 13,687 of the 16,695 mothers who gave birth in Britain in one week in March, 1946, 43% report their babies were still wholly breast-fed at about 2 months of age. However, in Southport 76% of the babies were reported totally breast-fed at 2 months, as compared with 15% in Lewisham. The incidence of breast feeding in Switzerland appears to be more nearly like that of the United States, since 25% of the babies are reported to be exclusively

breast-fed for 10 weeks and 10% are exclusively breast-fed after 6 months[9]. Breast-feeding studies done in Stockholm[32], Paris[1], and New Zealand[6] indicate decidedly higher rates for breast feeding than in the United States. The average baby in the Stockholm study is reported to be weaned at about 7 months; 49% of the babies in the Paris study and 46% of the New Zealand babies are reported to be still breast-fed at 6 months. Romero[75] states that in Mexico 92% of the city children and 98% of the country children are breast-fed. Commercial milk is so expensive there that the poor classes cannot afford to buy it.

It has long been known that *mothers' attitudes* toward lactation influence the course of lactation. Recently an objective statistical study[55] of this phenomenon shows that 74% of the mothers, who really want to breast-feed, later have enough milk for their babies as compared with 35% of the ambivalent group and 26% of the negative group. This study was done in a hospital where babies were with their mothers 6 times a day for almost an hour each time. The results should not be generalized to the many hospitals which routinely curtail the nursing times to such an extent that adequate milk production is almost impossible.

The *attitudes of doctors and nurses* who supervise breast feeding also influence its course. About 8 to 10 years ago statistics were published[29,83,87] which show that supplementary bottle feeding in the hospital and the use of only one breast at each feeding are practices which are associated with lactation failure. However, these practices continue to persist today in a great many hospitals. This inertia in applying the results of investigation is in striking contrast to the speed with which other research findings are adopted into medical usage. Breast feeding is a complex problem because it is easily influenced by cultural and psychological factors as well as by physical factors. A doctor's judgment about breast feeding is not only influenced by recent research, but also by such mundane matters as whether or not his own wife breast-fed his own children.

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PEDIATRICS

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IDIOPATHIC SCOLIOSIS

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THE statement once made that the treatment of idiopathic scoliosis is "a perpetual lesson in humility" still holds true to some extent. A part, at least, of the responsibility for the continued imperfect final results in the correction of idiopathic scoliosis has to be laid at the feet of the family and of the school physician, the pediatrician, and the school nurse. The spinal deviation may easily escape the mother's notice until a gross deformity exists, since the process does not usually begin until after the child has become independent in his dressing and bathing. Yet early detection of the spinal curve is the single most valuable aid in obtaining a good corrective end result. It not only prevents the severe curves which are most resistant to treatment, but also the associated psychic trauma, increase in morbidity, and shortened life expectancy that go hand in hand with the greater distortions. The disease certainly has a far higher incidence than is generally accepted, if one considers that in the 7-year period of 1928 to 1935, 1498 new cases of scoliosis presented themselves at the New York Orthopaedic Hospital and Dispensary[29], by far the largest number of which was of the idiopathic group. In Eaton's[7] experience, 80% of all scolioses belong to this variety, and his figure is not greatly at variance with that of any other statistics. This review article has been prepared to stress the importance of idiopathic scoliosis for the pediatrician and to evaluate the progress made in obtaining good end results with improved treatment.

It is beyond the scope of this paper to discuss technical and surgical details in the corrective and retentive treatment of the disease, especially since no physician, inexperienced in the handling of plaster jackets, should attempt to apply one, even as a temporary measure. More harm is done by the application of ill-fitting jackets than by the omission of any support.

Definition. Idiopathic scoliosis is a deformity primarily of the spine, in which a lateral deviation and rotation of the vertebrae toward the convex side of the curve are the chief components. As a result of the spinal distortion, secondary changes in the trunk, pelvis, and shoulders become part of the disease entity and will be discussed under symptoms and diagnosis. The etiology of this defect is *obscure*, as the name implies.

Etiology. Ever since the disease was recognized, the etiology has been the subject of many publications, but no real conclusion has thus far been drawn. Many of the writers skip over the etiology with the statement that we are dealing with an intrinsic muscle

imbalance. At present this has to satisfy, since little light has been shed on the true pathogenesis. There are certain factors we know at least to be of influence in its etiology, most important among them being sex and growth.

Consistently in all reports, the sex ratio is approximately 4:1, female to male. For example, in the 425 cases reviewed by the Research Committee of the American Orthopaedic Association of 1941, the sex ratio was 82% female and 18% male. In Ponsetti and Friedman's[15] series, the female sex predominance was even somewhat more pronounced with an incidence of 84% in girls. This certainly suggests a hormonal linkage in the etiology, and research along these lines is in progress at this laboratory.

The rapid increase in the curves generally occurs during the period of greatest spinal growth, which falls for boys between the ages of 12 and 16 years, and for girls between 11 and 15. Spinal growth is slow between the ages of 5 and 11 or 12, respectively, and even though the curvature may be detected in this age group, rarely does it progress rapidly until the sudden growth spurt appears. With the cessation of growth and usually even one year before the epiphyseal lines of the spine are closed, the progression in the curvature comes to a spontaneous halt.

This growth linkage has, in the last years, almost exclusively occupied the literature pertaining to etiology. Most of the theories advanced have as their basis the experimental work on the growth of the spine in 2-week old kid goats, done by Haas[11].

Bisgard and Musselman[5] explain the lateral spinal deformity on the basis of unilateral growth arrest due to an insult, most likely an epiphysitis, to one side of the epiphyseal plates. They do not believe the gravity of superincumbent weight to be more than a secondary contributing factor. Proof for this they find in the lack of structural changes in scoliosis developing during adult life. Were superincumbent weight mainly responsible for the production of atrophic vertebral bone changes, as a result of pressure, certainly the adult scoliotic should show as marked or greater structural changes. Added emphasis is put on this theory by the frequent lack of structural change in scolioses following empyema, in which the spine straightens out immediately after the contracting pleural scar is made to release its pull.

This theory certainly has as good a foundation as any thus far advanced and would put idiopathic scoliosis into the same category as Legg–Perthes' disease, which from its general behavior may well be true. Both diseases improve with rest, both have sex linkage, though it be opposite, and both, if treated conservatively, show improvement of the roentgenologic changes seen during active progress of the condition.

Two more authors should be mentioned in connection with growth as an etiologic factor in idiopathic scoliosis.

Arkin[2,3,4], as opposed to Bisgard and Musselman[5], holds superincumbent weight to be the most influential single factor in the production of idiopathic scoliosis. He believes the primary postural curve to start as a result of muscle imbalance or habitual faulty posture. The structural changes are then superimposed by the now asymmetrical force compressing the epiphyseal plates. As proof for his theory, he advances the fact that recumbency, which only removes gravitational forces, arrests the progress of the curve. Moreover, Haas[11,12] did not get epiphyseal growth arrest in his experimental animals unless the wire threaded through the epiphysis was tightened to produce pressure.

Seidler[25], on the other hand, believes that idiopathic scoliosis is just an exaggerated form of the physiological scoliosis everybody develops after the age of 6. By the time the adult reaches old age, some structural changes are always present as its result. A constant struggle evolves throughout life between the ever present deforming factor and the effort of the spine to remain erect. During the period of rapid growth, when the bone and epiphyseal plate are soft and easily molded, the spine of the tired, anemic, undernourished child succumbs to the deforming factor.

In contradiction of the theory, it may be added that it usually is a rather husky, well-nourished child that presents itself with scoliotic deformities. Anemias certainly are rarely seen.

Of less importance in the etiology of idiopathic scoliosis seems to be heredity. Some families are prone to develop scolioses, but the 1941 review of the 1941 Research Committee[19] shows that in only 7% of the cases are 2 members of the same family affected even in different generations.

Race seems to have no etiological influence.

Symptoms. If one considers in this disease the extensive body distortion, which jeopardizes most of the vital organs by compression, it is always surprising to realize how few and how late the symptoms are. It is the cosmetic deformity that brings the patient to the physician for correction in over 90% of the cases.

Next in frequency as the presenting symptom, and the only other one that needs to be mentioned, is pain, which rarely begins before the age of 14. This constitutes a late symptom, if one considers that 92% of the cases have their onset between the ages of 7 and 15. Other late symptoms are fatigue, weight loss, improper nutrition, poor respiratory reserve, increased morbidity, and even a shortened life expectancy in the severe deformities which remain uncorrected. One would expect to see in the severe curves, sometimes angulating well over 100°, an encroachment on the spinal cord with paresis or paralysis of the legs, with or without loss of control of bowel and bladder. Even in other forms of scoliosis this is a rare occurrence (only 28 cases were reported up to 1937: Heyman[13] and Ruhlin and Seymour[23]), but so far there are no reports of it in idiopathic scoliosis.

Inspection is the simplest and most effective method in establishing the diagnosis of scoliosis, if the child is seen in the office of the non-specialist. Ullrich[31], in a paper directed to the pediatrician, compiled clearly the signs to be watched for in the inspection examination, which can largely be carried out from a posterior view. In the erect position the scoliotic back is asymmetrical, the half of the back on the side of the convexity protruding more. This deformity can be demonstrated even better when the patient bends forward. At the same time it constitutes one of the helpful differential diagnostic points between a postural and structural deformity. The postural curve straightens itself when the back is bent forward, and the asymmetry disappears.

In approximately 80% of the cases of idiopathic scoliosis the shoulder on the side of the convexity is higher, on an average of ¼ to ½ inch, but there may be a difference of as much as 2½ inches. Likewise, the iliac crest (hip) is more prominent on the convex side of the curve, the deviation being about the same as that of the shoulder. The hip prominence is the result of a shift of the trunk as a whole toward the convexity which throws out of alignment the occiput, center of the shoulders, middle of the sacrum, and intergluteal fold. In the normal spine all these points and the spinous processes, of

course, lie in one straight perpendicular line.

The body, in a strong attempt to keep this alignment intact, compensates for a primary lateral curve, by secondary, usually smaller, curves. That the body does not always succeed in this effort is evidenced by the fact that 55% of the patients have a trunk list when first examined.

In scoliosis, as Kleinberg[15] points out, the vertical diameter of the trunk is always shortened, though it be little. However, there is at least one report in the literature in which a patient gained 11 inches in height after treatment by fusion.

The chest will get telescoped into the abdomen, and the lower ribs may hang below the iliac spines in cases of severe curvature.

Types of Curves. From a practical standpoint, a classification of the various curves encountered serves a purpose only where it is an indicative aid for treatment and prognosis. Two main lines are followed in subdividing idiopathic curves. According to the presence or absence of anatomical change in the vertebral body, one distinguishes between postural and structural curves. The postural curves show no associated changes in the bony structure of the vertebrae, indicating automatically the best response to therapy. According to the location of the primary curves, one encounters cervicothoracic, thoracic, thoracolumbar, and lumbar curves. The curve most frequently seen is the primary right thoracic (78 to 90%, according to different statistical evaluations), with a compensatory left lumbar deviation.

Ponsetti and Friedman[18] worked out, in detailed statistics, the prognostic significance of the site of the primary curve. They found that primary thoracic curves progress faster and reach greater excursions than any other type, while the primary lumbar C-curve (seen in 23.6% of their cases) was the most benign in treatment and prognosis.

In general, it can be stated that in idiopathic scoliosis, the site of the apex, the location of the curve, and the direction never change once they are established. Only the angle of the curve increases.

Roentgenologic Aspects. The Roentgen ray examination is an important aid in all phases of scoliosis work.

In Diagnosis. Establishment of the primary curve is a necessity prior to the institution of any treatment. In general, it is safe to assume that the curve a) with the largest diameter, b) in the middle position of 3, and c) most resistant to correction is the primary one. The only author taking exception to this ruling is Seidler[25], who thinks the lumbar curve always to be primary, even though it may be the more flexible one. He sees the rigidity of the thoracic curve as one born of necessity, resulting from its attachment to the thorax and its responsibility in keeping the body erect.

The *apex* of the primary curve is the vertebra showing the greatest amount of rotation, as evidenced in roentgenograms by the asymmetry of the lateral pedicles in relationship to the lateral aspects of the vertebral bodies. The rotation takes place toward the convex side of the curve.

Of importance is the *evaluation of the structural changes*, as far as they are shown in the Roentgen-ray picture. We find wedging of the vertebral bodies, most pronounced in the vertebrae near the apex of the curve; an inequality in the width of the intervertebral disc, which is narrowed down at the concave side of the deviation; osteoporosis, often limited to the apical part of the curve; and evidence of relaxed ligaments along the convexity.

We know from pathologic specimens that there are other structural changes,

such as atrophy of the posterior arch and of the lateral pedicle on the concave side of the curve.

IN TREATMENT. Before treatment can successfully be undertaken, a number of other Roentgen-ray studies are mandatory.

Determination of Flexibility of Primary Curve. This is established by taking films in the supine position with the spine in maximal left and right lateral excursion. In this manner, the corrigibility of both the primary and secondary curves is manifested. In plaster one can expect approximately 20% more total correction than on the film.

Pelvic Tilt Roentgen-Ray Examination. Goldstein[10] in his paper describes the procedure and its worth in detail. Most authors have accepted it as an invaluable aid in the determination of the maximal correction to be achieved. The method applies to the correction of the secondary lumbar curve. In the free sitting position (the hands must not be used for support), a block is put under the buttocks on the side of the lower hip to level the iliac crests. In this position the lumbar deviation will be fully compensated, if complete correction is possible. If this is true, one may attempt to overcorrect the principal curve slightly, allowing for an anticipated loss of correction of 10 to 12° in the end result. In case the secondary curve can only be partially corrected, the primary curve should not be pushed to full correction, since good body alignment then becomes the primary object. By superimposing in the proper manner the pelvic tilt film on the regular supine correction film, an almost perfect visualization of the total correction anticipated is obtained.

Extent of Primary Curve. Determination of the extent of the primary curve is of great importance when spinal fusion is scheduled. The end vertebrae are spotted in the following manner: a) They are the least rotated and the least wedged; the width of the intervertebral disc over its entire cross diameter remains almost constant. b) Lines drawn across the upper level of the upper-end vertebra and across the lower level of the lower-end vertebra should be parallel, and perpendiculars erected on these lines should bisect both vertebral bodies.

In doing this, at times it becomes difficult to separate one curve from the adjacent one at the point of transition. Vom Saal[33] offers the following suggestions: If lines are drawn through the center of the suspected end vertebrae parallel to their upper and lower borders, respectively, these lines form radii of the same circle. Lines through adjacent vertebrae will, in the same manner, form radii of a different circle.

Deviation of Curve. The angle of deviation prior to treatment, also of great prognostic importance, must be determined so that it can be used to establish at a later date the corrective and end results. It is, in addition, the means of accurate follow-up while the patient is under conservative therapy and during the postoperative period. The angle is established by erecting perpendiculars on lines drawn parallel to the upper plane of the upper-end vertebra and to the lower plane of the lower-end vertebra. The angle these lines form at their point of intersection is the angle of deviation.

An analysis of the 296 patients treated at the New York Orthopedic Hospital and Dispensary[28] showed the following pretreatment distribution of deviation angles over the period of 1928 to 1935: mild curves, 20 to 40°, in 52% of patients; moderate curves, 40 to 60°, in 20% of patients; severe curves, 60 to 80°, in 9%; and extreme curves, 80° and over, in 5%.

It would be valuable to compare these figures with a similar, at present unavailable, compilation of data for

the past 15 years, mainly to ascertain whether or not earlier detection of the curves has become the rule.

Marking of Vertebrae Prior to Fusion. During operations the surgeon needs a guide to the length and site of the fusion area. For his aid a film on which the apical vertebra is marked by lead or a needle is kept in readiness. From it he can count off and mark the vertebrae to be included in his procedure.

Evaluation of Growth Arrest. The best indication of spinal growth arrest is found in an ossified iliac apophysis, which appears after closure of the spinal epiphyses. The latter are much harder to visualize. The significance of this examination needs little emphasis, if one realizes that approach to growth arrest may spell the difference between safe conservative treatment and spinal fusion.

In Follow-up During and After Completion of Treatment. Repeated Roentgen-ray examination should be made to get an adequate follow-up during and after completion of treatment.

A patient under conservative treatment needs to be checked by roentgenograms at intervals of no more than 3 months. If this is neglected, a considerable increase in curvature may go unnoticed and the ideal time for fusion may be missed, while an improvement in posture may lull the patient and therapist into a false sense of security.

As a post-fusion follow-up, Roentgen-ray examination is a "must" at intervals of 3 months or less during the remaining period of active growth. While a loss of correction of 10 to 12° is the rule after the patient first becomes ambulatory, one beyond that figure is a danger signal and needs immediate, careful investigation. The single most common reason for rapid post-fusion loss of correction is a pseudarthrosis. Again by means of Roentgen-ray examination it is located prior to early surgical repair.

Treatment. As early as the 1890's, Hoffa established and emphasized the 3 main principles still applied in the treatment of idiopathic scoliosis. They are: 1) *mobilization*, 2) *redressment*, and 3) *stabilization*. To achieve the optimal spinal rehabilitation in all 3 of these phases is the aim of any therapy. Since this result cannot always be obtained, mobilization, the only 1 of the 3 that is not absolutely mandatory, frequently has to be sacrificed.

All techniques of treatment fall into 2 large subdivisions: *conservative* and *operative*. The utmost care has to be exercised in the selection of cases for either method, guided by knowledge of previous results and prognosis.

Anyone who has had close contact with the therapy in idiopathic scoliosis knows that although one strives for perfection, actually a good functional compromise is the best one can hope for in the large majority of cases. A perfect result, which means complete realignment of the spine combined with automatic, muscle-controlled stability and mobility, can only be worked for in postural scoliosis. Mainly for that reason and because optimal functional compromise does not have the same meaning to all authors, a great diversity of opinion exists as to the indications and contraindications for either method of treatment. In the following paragraphs, some of the generally accepted principles for either form of therapy will be outlined with a brief mention of the main variances encountered.

Conservative Treatment. Conservative treatment consists of the prescribing of exercises, symmetrical and asymmetrical, alone or in addition to supportive braces and jackets. The supportive measures may be applied following a period on a corrective frame, if indicated.

Indications. There are only 3 generally accepted indications for conservative treatment.

1. A postural curve can be healed by exercises alone as long as frequent Roentgen-ray check-ups, carried through the entire period of growth, show that there is no progression into a structural curve. The exercises have to be continued for a minimum of 2 years to prevent relapse.

Exercises alone have a place in the treatment of structural scoliosis only during the period of watchful waiting which the physician needs to size up the characteristics of the curve, immediately after the patient has sought his aid. The patient may show some postural improvement during that time, but the main advantage of this regimen lies in assurance of the patient's closer contact with doctor or institution.

2. A structural curve which starts near the time of growth arrest and shows no progression even while under observation may do well with conservative measures.

3. A mild structural curve appearing early in the period of rapid growth may be treated expectantly until evidence of progression occurs. According to Vom Saal[33] and Ponsetti and Friedman[18], these curves, if carefully followed, may be treated entirely with exercises. Goldstein[10], Eaton[7], and Seidler[27], however, like to add a well-fitting brace. The last mentioned author feels that exercises alone can never be of value. The muscles even in a postural curve are of necessity under maximal stress because of their natural attempt to maintain an erect position against the pull of deformity. If the additional strain of exercises is superimposed, they will give way altogether, and as a result the curve will progress rapidly. While resting the muscles in a well-fitting brace, however, proper exercises will maintain full back strength and aid in postural rehabilitation.

For a different reason Eaton[7] sounds a further word of warning against exercises. He cautions against exercises designed to decrease the rigidity of a curve, which may well constitute a defense mechanism established by the body to counteract the deforming forces. Increased flexibility may thus become directly responsible for an increase in the curve.

Correction and maintenance of the body alignment with the resulting cosmetic improvement, as would be expected, become the chief therapeutic objective of all conservative authors such as Steindler and Ruhlin[29], Kleinberg[15], Seidler[27], and Ponsetti and Friedman[18], all agreeing that the actual angle of a curve cannot be influenced by conservatism. The body fully aligned, however, the patient successfully hides when fully clothed a curve of up to 60 to 70°. The process of correction in alignment frequently has to include an initial period of recumbency during which the patient on a convex corrective frame is subjected to traction in the longitudinal axis. To this Kleinberg[15] adds a lateral pull at the apex of the curve directed toward the concave side.

With the exception of Seidler[27], all writers attach a headpiece on their corrective jackets to stabilize the head and exert some traction on the superior spine. Steindler and Ruhlin[29], going further, enclose the hip or thigh on the convex side in a leg extension piece to immobilize the pelvis against the trunk, in order to prevent secondary decompensation. In this process, the primary curve slowly extends up higher into the cervicothoracic region or downward into the lumbar spine. (This reasoning is contradicted by Ponsetti and Friedman[18].)

Seidler[25], believing the lumbar curve to be the primary one, limits his endeavors only toward its correction, applying a jacket that reaches no higher than the apex of the thoracic curve. The secondary curve (thoracic), he states, straightens automatically. His patients are never subjected to more than a total few days of recumbency for initial correction of the lumbar curve by long axis traction and excellent end results are seen. The long years of constant therapy, he feels, are compensated for by the lack of a hospitalization period. All the conservative authors agree to the need for a well-fitting support worn constantly during the entire period of growth.

Operative Treatment. *Indications.* All workers in the field, whether belonging to the conservative group or not, do recognize certain features in the curves of idiopathic scoliosis which demand fusion. These indications are: 1) established progression of a curve in a growing child; 2) pain and/or fatigue as the result of the deformity; 3) severe curve associated with severe body imbalance, whether or not the patient is in the active growth period. These three axioms include all the cases in which conservative treatment has failed to achieve the desired alignment or its maintenance.

Correction. By any established method properly applied, maximum correction of a curve is obtained while resorting to relatively little force at negligible discomfort to the patient in a short period of time, weeks rather than months. Force and time beyond that point will only lead to trouble without any further corrective benefit. The emphatic realization of these points is of greatest importance to any physician doing corrective scoliosis work.

The best generally accepted corrective appliance in current use is the turnbuckle jacket by Risser, designed and first used in 1926. The facts that in the last 15 years it has undergone only minor revisions and has retained preference in the entire field best speak for its efficiency. Though theoretically simple, its proper application calls for skill and experience. While it is molded to the body, the patient is suspended in extreme lateral flexion in line with the concavity of the curve. The hinges are incorporated into the plaster anteriorly and posteriorly over the apex of the curve, and the turnbuckle attachments are put in laterally at the height of the pelvis and the upper chest, respectively, over the convexity of the curve.

Slow tightening of the turnbuckles after the cast is dry and properly wedged can begin a few days later and will bring about maximal correction over approximately 2 weeks.

A few writers make an additional separate effort in derotation, which is the component most resistant to correction. It is well to note in this connection that no direct relationship between the severity of these 2 deformity factors exists. Special efforts at derotation, for example, were described in the corrective treatment outlined in 1941 by Steindler and Ruhlin[29]. Similarly, after maximal correction of the lateral deviation has been obtained in the Risser jacket, Vom Saal[33] under special precautions separates the upper portion of the cast and rotates it so that the shoulder on the convex side of the curve is brought forward until it is level with the other. More recently, Thomas[30] in the same attempt has resorted to a combination of traction in the longitudinal axis and lateral pressure over the apex of the curve and over the pelvis and upper thorax on the opposite side of the body. Progress of correction is checked every 2 weeks by Roentgen-ray examination until the maximum is obtained; the patient then remains in the apparatus for an

additional number of months. Out of 15 cases, 12 showed good corrective end results of the lateral deviation but generally little derotation.

In summary, it may safely be stated that thus far all attempts at separate rotation correction have been futile, perhaps because understanding of this composite deformity is lacking. As far as it is now known, even in its severest form it is solely of cosmetic, and not of functional, significance. At present the only satisfactory way of dealing with its most disfiguring manifestation, the razor back, is a partial posterior thoracoplasty, which renders good cosmetic results, without functional defects.

Fusion. Nearly all authors fuse the spine after correction has been completed. However, in a number of cases now, Shands[26] and his group at the Alfred I. duPont Institute have preceded their corrective measures by spinal fusion, thus far with most favorable results. Reversing in this way the usual order of procedure presents a number of advantages: 1) The patient, who as yet has not been subjected to the strain of correction, tolerates the operation better and morbidity is reduced to a minimum; 2) the surgeon, who does not have to work through a window in the cast, has a better exposed operative field, can proceed with greater dexterity and speed, and can readily obtain autogenous cancellous bone from the ilium to reinforce the fusion; 3) the danger of wound infection is minimized.

The patient is put in the corrective jacket a week after completion of the last stage of the fusion, well before the time the fusion graft starts to solidify. Up to the time of this publication no untoward effects have been observed, though a considerably longer follow-up for full evaluation is needed.

The length of a fusion is determined by the length of the primary curve: All vertebrae belonging to the primary curve have to be included. Even if only one (at either end) is excluded, postoperatively it will become the seat of further curving. Some authors prefer a fusion area which extends one or two vertebrae beyond the primary curve for greater solidity[19,25]. If lumbar vertebra 5 is partially sacralized, it should be included in the fusion area, since such a vertebra may later give rise to pain.

In the 1941 review by the Research Committee[19] the shortest primary curve comprised 4 vertebrae, with a usual range of 6 to 9 vertebrae. Accounting together for 57% of the cases, the apex of the curves was most frequent at thoracic vertebrae 9 and 8 and lumbar 1.

It is important not to fuse more than 4 or 5 vertebrae in one stage, to avoid shock. The mortality rate decreased in the New York Orthopaedic Hospital from 1.9% to 0.6% as a result of that realization.

The Hibbs fusion described in 1916 and its modifications are still the fusion operations of choice. In most instances the bone chips obtained in preparing the fusion bed do not suffice, and bone from donor sites, usually the iliac crest or tibia, has to be added. Outland and Corn[17] reported the use of long tibial grafts providing mainly easier visibility of graft–fractures. In any event, the concave side of the spinal curve has to be grafted, but as a safety measure some orthopedic surgeons lay down grafts on both sides of the spinous processes.

Postoperative Treatment. The patient has to be kept recumbent in the original corrective jacket for the first 3 months postoperatively. The jacket should incorporate for stabilization of the pelvis at least the hip and thigh on the convex side of the primary curve. For greater assurance of immobilization in the fully corrected position while the graft begins to mature,

Shands[26], however, prefers to include the whole leg on that side in addition to the opposed hip and thigh.

After 3 months an ambulatory plaster jacket with the same headpiece replaces the original one. Only after this minimum period of 6 months in a well-fitting plaster jacket has elapsed may the patient be fitted with a brace, which has to be worn at all times in the erect position for at least another 6 months. Although in the above-cited statistical evaluation[19] no further benefit from longer immobilization could be demonstrated, Goff and Aldes[9] recommend a minimum of 8 months in plaster jackets and then for an additional year have their patients wear a celluloid jacket.

A word of caution regarding the ambulatory jacket and brace is in order. Both these structures have to be heavy enough to uphold postoperative correction even when the superincumbent weight is suddenly added to the pull in favor of the deformity exerted by the contracted muscles.

In the roentgenologic section of this paper frequent postoperative follow-up films are mentioned as being mandatory. This point is reemphasized here.

An entirely new way of treating a progressive idiopathic scoliosis deserves brief mention. Rieth, Hopkins, and Dunlap[21] recently published a preliminary report of their first case of scoliosis treated by unilateral stapling of the epiphyseal plates involved in the primary curve, recalling the experimental work of both Haas[11,12] and Bisgard and Musselman[5]. A transpleural approach was used, with the cooperation of a thoracic and an orthopedic surgeon. At the time of publication there had been no follow-up report.

It seems appropriate to sum up the entire subject of therapy in the formulation of a definition of effective therapy: Treatment is effective if, when started during active progression and growth, it is able to maintain correction and to prevent progression until growth has ceased.

Complications of Operative Treatment. The complications of operative treatment are generally few and mild. A few only need be mentioned. *Pseudarthrosis* constitutes one of the most feared postoperative mishaps. Usually it is the result of too short a fusion or faulty preparation of the fusion bed. Once it has occurred, only early detection and repair can prevent great or even complete loss of correction. This again puts emphasis on the necessity for close Roentgen-ray supervision in the postoperative period. In the report of the Research Committee of the American Orthopaedic Association[19], pseudarthrosis followed 28% of the fusions. The average loss of correction in these cases was only 21°, as against 15° in the remaining cases, thanks to early surgical repair. As a result of better judgment in all phases of fusion work the incidence of pseudarthrosis is decreasing. Of *wound infections*, only the deep ones are of consequence, and since the advent of antibiotics are fairly easily controlled.

Decubitus ulcers not only can be bothersome but may lead to regrettable and deforming scars. As with all casts, persistent localized pain should be immediately investigated and treated. It should be remembered that, due to trophic changes, pressure sores become painless after a few days. *Transient brachial palsy* as a result of pressure occurs with some frequency and is always relieved by cutting out the cast.

End Results and Prognosis. Conservative Treatment. The best evaluation of results after conservative treatment is found in the Report of the Reseach Committee of the American Orthopaedic Association[19]. Patients treated only with gymnastics presented the most discouraging results. With sym-

metrical exercises, 53% of the patients showed progression of their curves, while with asymmetrical exercises this figure rose to a staggering 75%.

The over-all evaluation of results of treatment, exclusive only of the cases treated by a combination of Risser jacket and fusion, showed an average final improvement in the curve of only 15°; 72% of all cases treated conservatively lost their once attained correction completely as compared to 30% of the patients treated by Risser jacket and fusion.

More recently only the end results of small series of cases have been published representing a great variety of conservative therapeutic methods (Steindler and Ruhlin[29], Seidler[25], Kleinberg[15], and Ponsetti and Friedman[18]). All show full maintenance of correction in about 80% of the cases with adequate follow-up. All agree that the most important factor in achieving such favorable results is the careful selection of cases, as is well illustrated in the group of 394 cases treated conservatively by Ponsetti and Friedman[18].

Operative Treatment. The earliest end-result statistics were published by the group of physicians at the New York Orthopaedic Hospital and Dispensary[6,8,14,22,27,28], who started evaluation of their cases in 1914, about the time of the 1st fusion. It is true that all cases of scoliosis, regardless of etiology, are included. However, since of the total 725 cases reported between 1914 and 1935, 382 (52.75%) had idiopathic curves, the results can still be accepted in this context to illustrate that improvement in the development of techniques and in the critical selection of material for each therapeutic procedure goes hand in hand with an improvement in the final results.

For example, in the group treated from 1914 to 1919, only 23.5% of the patients maintained even a 5 to 15° correction, while in the next period, 1919 to 1927, this figure rose to 42°. The advent of the Risser jacket, the first really effective method for correction and for maintenance of position after fusion, brought about a far more striking boost to the permanent result. In the consequent period of 1928 to 1935, of the patients treated with fusion, 80% maintained their original correction in mild, 49% in moderate, and 30% in severe curves. Considering improvement both in posture and in the curve as shown by Roentgen-ray study in this last-mentioned 7-year period, a round 80% had good or excellent results. The improvement in these statistics was not thought to be entirely due to the introduction of the Risser jacket; it was also due to better judgment in selecting the proper fusion area, resulting in fewer pseudarthroses, and to the wearing of proper support postoperatively for at least a year.

The importance of the skill and experience of the surgeon becomes apparent when the above data from 1928 to 1935 are compared roughly with those shown in the best statistical analysis published since 1935 by the Research Committee American Orthopaedic Association 1941[19]. In the latter the analysis deals with results obtained in 16 clinics spread widely over the United States, many of the patients being drawn from rural communities, while in the former the analysis deals with cases seen in one clinic, where the interest in scoliosis has been most active, where many hundreds of cases have been treated over the last 3 decades, and where the patients are largely residents of New York City. Thus we are confronted with the average end result in the correction of 27% on the one hand, against 53% on the other, while in both series the treatment method employed was the best,

a combination of Risser-jacket correction and fusion.

Although the discrepancy in results must, at least in part, be attributed to the above-outlined factors, one wonders how great a role, in addition, is played by the unawareness of the disease and its importance on the part of the practitioner and the average population.

Though the objective figures quoted certainly are discouraging, 72% of the patients after treatment by fusion and Risser jacket considered themselves improved, and clinically 76% showed fair to excellent results.

The only other large and very good statistical analysis published since 1941 by Ponsetti and Friedman[18] is not concerned with end results. The lack of a good statistical analysis of a large number of cases of idiopathic scoliosis treated over the past 10 years is painfully striking. Until such a compilation of data is prepared, there is no way of evaluating the progress made in the end results of the various forms of therapy over that period of time.

Prognosis. The prognostic importance of the age of onset and the rapidity of progression of a curve has been well established for many years, both these factors being directly proportionate to the final outcome. By far the majority of angulations over 80° have had their onset under the age of 10 years.

Ponsetti and Friedman[18], in their prognostic analysis, emphasize two more factors with similar significance: 1) the pattern of the curve, and 2) the severity of the structural changes, especially the osteoporosis and ligamentous relaxation.

Prevention. From this review, one conclusion can be drawn without hesitation: The single most valuable weapon available to combat the severe, unsightly, and treatment-resistant forms of idiopathic scoliosis is prophylaxis. The slighter the curve and the shorter the duration when the patient is first seen, the better is the chance of good and possibly perfect end result.

Ideally, all curves of idiopathic scoliosis should come under medical observation while they are still only postural and should be treated by fusion as soon as progression is well established. (The fear of many surgeons of fusing a spine below the age of 10 years certainly no longer has a good foundation, since, as Goldstein[10] states, the flexible spine in the very young is more amenable to fusion and gives a more solid result). However, conservative treatment alone would probably not suffice to deal with all curves, since even under close observation some postural curves will become structural, due to an as yet unknown basic etiological difference.

To make prevention at all effective, education of the general population is needed. Two harmful and false pieces of information are, for example, still prevalent: 1) Children will outgrow small or moderate curvatures, and 2) there is no effective treatment for children with scoliosis.

To fight such ignorance the public needs to be confronted with up-to-date, practical, and illustrative material in the form of literature, films, and lectures. As already pointed out, even our medical statistics are sadly outdated and sketchy. In addition, it would be a great aid if all adults in contact with children and in positions of responsibility could be taught the simple art of back inspection or at least could be impressed with the necessity of frequent examination. Every growing child should be examined, preferably by a physician, at least once every 6 months. This should be as much a part of a routine school examination as looking at the tonsils.

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ERRATUM

The editor and the Authors of the article, "Vitamin D Intoxication," appearing in the April, 1951, issue of the Journal (p. 369) regret exceedingly the error made regarding Darthronol. It was stated that this multivitamin preparation is available without prescription. The authors state: "We knew that at least one of the patients in our series had obtained Darthronol without prescription but did not realize that the druggist had been at fault in issuing it to him. We were not aware of the fact that the legend states that a prescription was required. . . . Their product carries a label stating that it should be dispensed only on the prescription of a physician. . . . It is unfortunate that such multivitamin preparations contain potentially toxic doses of Vitamin D in contrast to non-toxic doses of other vitamins without any indication to druggist or patient that the dose of Vitamin D is potentially toxic."

PROCEEDINGS OF

The Physiological Society of Philadelphia

SESSION OF APRIL 17, 1951

A Turbidimetric Method for Estimation of Polyvinylpyrrolidone in Body Fluids. J. G. REINHOLD, Ph.D., and C. A. J. VON FRIJTAG DRABBE (Pepper Lab. of Clin. Med. and Dept. of Res. Surg., Univ. of Penna., Phila.) Polyvinylpyrrolidone (PVP) reacts with aqueous phenol to give a turbid suspension that may be used for estimation of the PVP concentration in serum and urine. The turbidity formed increases with the concentration of phenol and becomes maximal at a phenol concentration of 1.1 per cent. The reactivity of PVP in serum and urine remains unchanged on standing 24 hours or longer, provided the pH is maintained between 4.8 and 5.6. A pH of 4.8, maintained by means of a 0.1 Molar acetate buffer, has been found optimal for serum measurements, and an M/15 phosphate buffer of pH 5.6 for determinations in urine. A rectilinear relationship between turbidity and PVP concentrations exists up to 300 mg. per 100 cc. in either serum or urine. Measurements may be made directly on serum without removal of proteins provided a blank and standard are prepared with serum obtained before the administration of PVP.

Blood Flow and Oxygen Consumption of the Human Brain during Sleep. R. MANGOLD, M.D. (by invitation), L. SOKOLOFF, M.D. (by invitation), P. O. THERMAN, M.D., E. H. CONNER, M.D. (by invitation), J. I. KLEINERMAN, M.D. (by invitation), and S. S. KETY, M.D. (Dept. of Physiol. and Pharmacol., Grad. Sch. of Med., Univ. of Penna., Phila.) Cerebral blood flow and oxygen consumption of 8 healthy young men were measured by means of the nitrous oxide method during natural sleep. To facilitate sleep the subjects were kept awake for approximately 20 hours prior to each study which consisted of a determination before and another during sleep. The level of wakefulness or sleep was evaluated on the basis of continuous E.E.G. recordings. On most subjects unable to fall asleep 2 consecutive determinations were performed as a control of variations between repeated measurements.

In 8 successful studies during sleep the following results were obtained. Cerebral blood flow increased from a mean control value of 58.0 to 63.7 cc./100 gm./min., representing a significant increase ($p < 0.01$), which is also significantly different from the variations of this function observed in 2 consecutive control determinations (from 61.4 to 57.2 cc./100 gm./min. ($p < 0.02$). Mean cerebral arteriovenous oxygen difference was 5.3 vol. per 100 cc. during sleep and 5.95 vol. per 100 cc. in all subjects awake but fatigued, a statistically significant difference ($p < 0.01$). Sleep did not produce any significant change in cerebral oxygen consumption which averaged 3.33 cc./100 gm./min. during sleep compared to the mean of 3.36 found in the controls of the same study with the subjects awake, or the mean of 3.49 obtained from all waking but fatigued subjects.

Hepatic Blood Flow and Hepatic Carbohydrate Metabolism in Man during Fainting. S. Sherlock, M.D., A. G. Bearn, M.D., B. Billing, Ph.D., and O. G. Edholm, M.D., (Dept. Med., Postgrad. Med. Sch. of London, England). Fainting was induced in 6 subjects by the application of venous occlusion cuffs to the thighs with or without additional venesection. In 2 other subjects fainting was spontaneous. Using the hepatic vein catheterization technique, changes in hepatic blood flow, splanchnic output of glucose and capillary blood glucose concentration, blood lactic acid concentration and splanchnic uptake of lactic acid, and splanchnic oxygen consumption were determined. During the period of hemorrhage hepatic blood flow diminished and there was evidence of splanchnic vasoconstriction. At the time of fainting hepatic blood flow fell but there was an apparent splanchnic vasodilatation. This was followed by a further period of splanchnic vasoconstriction. Hepatic blood flow remained low even when the systemic blood pressure had returned to normal values.

Hepatic glucose output increased at the time of fainting with a resultant rise in concentration of the capillary blood glucose. Concentration of blood lactic acid increased after fainting, and the excess lactic acid was shown to be taken up by the liver. Hepatic venous oxygen unsaturation diminished greatly at the time of fainting, so that, despite diminished hepatic blood flow, the splanchnic oxygen consumption was maintained.

The possible role of epinephrine, *nor*-epinephrine, posterior pituitary hormone, and other factors in producing these results must be considered.

A Continuous Recording Automatic Bubble Flow Meter. A. Sokalchuk, M.D., Arnold S. J. Lee, A.B., and Keith F. Killam, B.S. (Res. Div. Smith, Kline & French Laboratories, Phila.). A continuous recording automatic bubble flow meter was designed and adapted to recording coronary blood inflow in the anesthetized animal. Impulses derived from photoelectric timing of the reciprocal transit of a single air bubble introduced in a system containing a loop of plastic tubing of known volume are utilized to activate a specially designed disc valve. The valve action selects in alternation one pair of the 2 branches into which both input and output tubes are divided and thus directs the forward motion of blood so as to oscillate the air bubble, in the above-mentioned calibrated tubing, between 2 photocells. Each activation of the disc valve by the photocell response to the air bubble transit is also utilized to operate a signal magnet. Continuous automatic recording on either smoked-paper or ink-writing kymographic instruments is thus obtained. A single air bubble will operate the device continuously for periods of about 1 hour. During this time the air bubble is gradually reduced in volume, due to progressive absorption by the blood, introducing a small error. This error ultimately reaches the order of approximately 1% at the time a new air bubble is usually introduced. No provision is made for maintaining constant temperature.

Many applications of the presented valve-switching principle are apparent in various fields of flow measurements.

BOOK REVIEWS AND NOTICES

THE DIAGNOSIS AND TREATMENT OF ENDOCRINE DISORDERS IN CHILDHOOD AND ADOLESCENCE. By LAWSON WILKINS, M.D., Assoc. Prof. of Pediatrics, The John Hopkins Univ., The Harriet Lane Home, The Johns Hopkins Hosp., Baltimore, Md. Pp. 408; 411 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $13.00.

HERE is an authoritative yet at the same time most practical text and reference on pediatric endocrinology, based on Dr. Wilkins' many years of observation and reflection on endocrine problems at the Harriet Lane Home of the Johns Hopkins Hospital. There are a wealth of illustrations, a beautiful format, a lucid style, and a carefully selected bibliography. Wherever feasible the chapters have been constructed to emphasize differential diagnosis. The one on Sexual Infantilism, for example, discusses differentiation from delayed adolescence, classification and diagnosis, sexual infantilism of neurogenic origin, pituitary hypogonadism, primary hypoovarism, primary testicular deficiency, and treatment of sexual infantilism. The author's attitude toward treatment is conservative and sensible. Hormone preparations are as a rule advised only for specific overt deficiencies. Dietary obesity would seem a little more difficult to control than indicated here. All in all, a most valuable contribution. I. W.

ATLAS OF HISTOLOGIC DIAGNOSIS IN SURGICAL PATHOLOGY. By KARL T. NEUBUERGER, M.D., Prof. of Pathol., and WALTER T. WIKLE, M.D., Asst. Prof. of Pathol., Univ. of Col. Sch. of Med. Pp. 460; 880 ills. Baltimore: Williams & Wilkins, 1951. Price, $11.00.

TRYING to acquire a knowledge of pathology by studying an atlas of cytopathology is a little like trying to guess the plot of a drama by one quick peek at the stage through a keyhole. The study of morphologic change is one of the most complex branches of medicine, and even in "classic" cases the cytologic variation may approach the infinite. Dr. Neubuerger has attempted the enormous task of presenting a minimum of these variations by static photographs. Dr. Wikle has contributed a section on exfoliative cytology.

There are two 3½ x 3 inch photomicrographs on each page with a very short descriptive text for each figure. The magnification of many of the illustrations is so low that this Reviewer considers them to be of questionable value. The selection of "typical" examples is a personal matter and the author has the right to include whatever he chooses, but this Reviewer would have omitted a number of figures. The nomenclature, the Author states in the preface, is that which is in general use. The appropriateness of the terms "spindle cell sarcoma, myatonia congenita, neurinoma, and neurogenic sarcoma" and others for the figures to which they are applied is questionable.

Inside the jacket, the publishers state, "When you must make a histopathologic diagnosis, of whatever part of the body, you are sure to find it amply covered in this atlas". It is questionable whether the Author shares this enthusiastic conviction. He states in the preface: (The book) "should furnish the aspiring histopathologist as well as the morphologically-interested clinician, with practical information". The Reviewer endorses this motive heartily, but he believes most readers agree that this group should not be making "histopathologic diagnoses". The book has a very limited use for the trained pathologist. Unfortunately it suffers in comparison with two other atlases currently appearing in the medical book market, "Color Atlas of Pathology," prepared by the U. S. Naval Medical School (over 1000 figures in full color), and "Atlas of Tumor Pathology," prepared by the Armed Forces Institute of Pathology which, when completed, should reach nearly 2000 pages on tumors alone. Dr. Neubuerger's book has the advantage of being somewhat less expensive. E. A.

SURGERY ORTHODOX AND HETERODOX. By SIR WILLIAM HENEAGE OGILVIE, Guy's Hospital, London. Pp. 241. Springfield, Ill.: Charles C Thomas, 1950. Price, $4.00.

IT is a pleasure to recommend this volume of stimulating and provocative addresses. Since the author on occasion makes his point by hyperbole the readers must have a critical attitude toward the contents, but all of the points bear thinking about and lead the reader inevitably to an attitude of self examination.

This Reviewer does not agree with many of the author's statements about American surgery and is sure that a less superficial examination of our clinics and methods of work would modify his critical generalities. However, it would not be a bad idea to make this book required reading for every teacher of surgery in our schools of medicine.

I. R.

PHYSIOLOGY OF THE EYE. CLINICAL APPLICATION. By FRANCIS HEED ADLER, M.D., Prof. of Ophthalmology, Univ. of Penna. Pp. 709; 319 ills., 2 in color. St. Louis: C. V. Mosby, 1950. Price, $12.00.

THIS book is the best in its field, written by a worthy author whose early training in physiology has enabled him to keep abreast with the advances in this subject. This ability has permitted him to extract most of the best, and to reject the large volume of less valuable material which is in the literature. The writing is lucid, and the organization is correct. The reader is reminded that ocular physiology is in its infancy and much of the material will be subject to change when knowledge in this field becomes more advanced. The profession owes Doctor Adler much for his efforts in the preparation of this very satisfying book.

G. G.

HARVEY CUSHING, SURGEON, AUTHOR, ARTIST. By ELIZABETH H. THOMSON. Foreword by JOHN F. FULTON. Pp. 347; 11 ills. New York: Henry Schuman, 1950. Price, $4.00.

THIS comparatively short account of the life of Harvey Cushing forms a very pleasing supplement to Dr. John Fulton's large and comprehensive biography. It is to the credit of Miss Thomson that her book is in no sense a condensation of the larger volume, for she has contrived to picture this great surgeon and scientist in a somewhat different light from that chosen by Dr. Fulton. For this purpose a considerable amount of new material, in the form of letters and documents, was available to her, and with their help and her sensitive approach she has managed to tell the story of Cushing's life by dwelling on his complex personality rather than by describing in detail his scientific accomplishments.

One can scarcely conceive of a task that was more challenging and at the same time had greater fascination. Cushing was endowed with a brilliant intellect, but furnished with very unstable emotions. In addition to these qualities he was highly talented. His mind was as sharp and as cold as a steel blade when directed to the solution of a scientific problem, but when it came to human relationships, his emotional responses were as flighty and as unpredictable as an April day. Miss Thomson develops with remarkable insight these personal qualities. He possessed a charm that at times was irresistible, and the devoted care that he gave his patients could be unbounded. But his temper was like quicksilver, for at one moment he might cut one of his assistants to the quick by his sarcastic criticism and at the next almost embarrass him with kindness.

In the many viscissitudes of his Quixotic existence his wife was of great assistance to him, and in this volume considerable stress is laid on his intimate relations with the members of his own family and with his close friends.

Cushing's eminence as a surgeon and a scientist, the importance of his researches to the advancement of medicine in general, and the recognition of his accomplishments through the bestowal of innumerable honors have become very familiar, but now Miss Thomson has contributed a sympathetic portrait of the man, drawn with such comprehension and sensitiveness that it cannot fail to attract and interest the general reader as well as the doctor and student. W. L.

NEW BOOKS

Biological Antioxidants. Edited by COSMO G. MACKENZIE, E. V. JENSEN, and RALPH HOLMAN. Pp. 181; ills. New York: Josiah Macy, Jr., Found., 1950. Price, $3.25.

Weitzel's Deutsches Obst und Gemüse in der Ernahrung und Heilkunde. By DR. W. HEUPKE. Stuttgart: Hippokrates - Verlag Marquardt & Cie., 1950. Price, DM 9.50.

Beiträge aus der Hormon- und Vitaminforschung. By DR. ARTHUR JORES and DR. HERMANN SCHROEDER. Pp. 80; 2 ills. Stuttgart: Hippokrates-Verlag Marquardt & Cie., 1950. DM 1.60.

History of the Woman's Medical College, Philadelphia, Pennsylvania, 1850-1950. By GULIELMA FELL ALSOP, M.D. Pp. 256; 6 ills. Phila.: J. B. Lippincott, 1950. Price, $4.00.

Occupational Factors in the Aetiology of Gastric and Duodenal Ulcers. By MEDICAL RESEARCH COUNCIL. Special Report Series No. 276. London: His Majesty's Stationery Office, 1951. Pp. 96. Price, 2s.6d.

Dimensional Analysis for Students of Medicine. By HAROLD A. ABRAMSON, M.D. Pp. 41. New York: Josiah Macy, Jr. Foundation, 1951. Price, $1.00, single copy.

Human Engineering. Edited by LAWRENCE E. ABT. Pp. 160; ills. New York: New York Academy of Sciences, 1951. Price, $2.75.

Wege vergleichender Therapie in der inneren Medizin. By ROBERT E. MARK. Pp. 418; 126 ills. Munich: Urban & Schwarzenberg, 1950. Price, DM 26.00.

Neurology and Psychiatry in General Practice. Edited by HENRY R. VIETS, M.D., Lecturer in Neurology, Harvard Medical School, in collaboration with C. CHARLES BURLINGAME, M.D., CLARENCE B. FARRAR, M.D., and Z. M. LEBENSUHN, M.D., Pp. 150. New York: Grune & Stratton, 1950. Price, $3.50.

THIS little book is based on the discussions at the Clinical Session of the American Medical Association, midwinter meeting in 1949. It is not intended to be a complete treatise on the subject but attempts to set forth enough to give the general practitioner a helpful insight into the present state of knowledge of some neurological and psychiatric conditions and their treatment by modern methods. W. P.

Blood Clotting and Allied Problems. Transactions of 3rd Conference, Jan. 23, 24, 1950. Edited by JOSEPH E. FLYNN, M.D., Dept. of Pathology, Coll. of Phys. and Surg., Columbia Univ. Pp. 224; 52 ills. New York: Josiah Macy, Jr., Foundation. Price, $3.00.

Typhoid and Paratyphoid B Carriers and Their Treatment. By TH. M. VOGELSANG, Prof. of Bacteriol. and Serology, Univ. of Bergen and Director, Gade's Institute, Bergen, Norway. Pp. 368; 3 figs. Bergen: University of Bergen, 1950.

An Introduction to Universal Serologic Reaction in Health and Disease. By REUBEN L. KAHN, D.Sc., Univ. of Mich. Med. School and Hosp., Ann Arbor, Mich. Pp. 158, 113 charts. New York: The Commonwealth Fund, 1951. Price, $3.50.

Health of Ferrous Foundrymen in Illinois. By U. S. PUBLIC HEALTH SERVICE AND ILLINOIS DEPT. OF PUBLIC HEALTH. Pp. 130. Washington, D. C.: Federal Security Agency, Public Health Service, 1950. Price, $0.75.

Jahresringe. Innenansicht eines Menschenenlebens Soetbeer. By ALFRED E. HOCHE. Pp. 260; 1 ill. Munich: J. F. Lehmanns Verlag, 1950. Price, 7.50 and 9.50 DM.

Hypnosetherapie und psychosomatische Probleme. By FRANZ ADREAS Völgyesi, Dr. Med. Pp. 203. Stuttgart: Hippokrates-Verlag (Marquardt & Cie.), 1950. Pp. 203. Price, DM 8.25.

Sinn und Wesen einer Ganzheitsmedizin: Ziele und Aufgaben der Kurse für Ganzheitsmedizin Reform des Arztlichen Schrifttums für den Praktiker. By DR. WERNER ZABEL. Band 1. Pp. 84. Stuttgart: Hippokrates-Verlag Marquardt & Cie., 1950. Price, DM 1.60.

Pulmonary Ventilation and its Physiological Regulation. By JOHN S. GRAY, M.D., Ph.D., Northwestern Univ. Med. Sch. Pp. 82; 14 fig. No. 63, American Lecture Series. Springfield, Ill., Charles C Thomas, 1950. Price, $2.00.

THE control of pulmonary ventilation is explained in a clear fashion. The responses of the respiratory system to abnormal states such as anoxia and acidosis are described. This is excellent reading for the student of medicine and the anesthetist, as well as for the physiologist. J. L.

Chronic Ulcerative Colitis (Thrombo-Ulcerative Colitis), American Lecture Series 101. By J. ARNOLD BARGEN, M.D., Division of Medicine, Mayo Clinic. Pp. 62; 3 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $2.00.

Psychosomatic and Suggestion Therapy in Dentistry. By JACOB STOLZENBERG, D.D.S. Pp. 152. New York: Philosophical Library, Inc., 1950. Price, $3.75.

THE author has written an introductory chapter which is sound in the modern psychodynamics of psychosomatic disease. Following the introduction, Dr. Stolzenberg has given two excellent chapters on many aspects of the patient's attitude toward dentistry and the attitude of the dentist himself toward his patient and his practice. Also included are emotional factors in dental problems such as peridontal disease, bruxism, and gingivitis.

The last two chapters devote more space to the use of hypnosis in dental practice than anyone could use except the dentist with special training in hypnosis. However, this is a book which dentists should definitely be reading. The bibliography and index are extensive. O. E.

Symposium on the Healthy Personality. Edited by MILTON J. E. SENN, M.D., Dept. of Pediat. and Psychia., Sch. of Med., Yale University. Pp. 298. New York: Josiah Macy, Jr. Found., 1950. Price, $2.50.

THIS volume reports the transactions of special meetings of a conference on infancy and childhood, June 8-9 and July 3-4, 1950, in New York, N. Y., participated in by 43 outstanding leaders in the field of child psychology, psychiatry, pediatrics, and allied fields. Three main themes covered are: Growth and Crises of the Healthy Personality, led by Eric H. Erikson; Constitutional and Prenatal Factors in Infant and Child Health, led by Ashley Montagu; and Toward a Social Psychology of Mental Health, led by Marie Jahoda. Reprints of the final reports on these topics were supplied to the Fact Finding Committee for distribution to leaders of discussion groups during the Whitehouse Conference, 1950. The material covered in this volume represents the latest thinking of leaders in child development on the rearing of an emotionally healthy generation. It is valuable reading. O. E.

Histamine Antagonists. By FREDERICK LEONARD AND CHARLES P. HUTTRER, Warner Inst. of Therap. Res., New York. Pp. 122; 48 tables. Washington, D.C.; National Research Council, 1950. Price, $1.50.

Primer on Fractures. By COMMITTEE ON FRACTURES, AMER. MED. ASSN. Pp. 109; 48 ills. New York: Paul B. Hoeber, 1951. Price $2.00.

Fainting, Physiological and Psychological Considerations. By GEORGE L. ENGEL, M.D. Univ. of Rochester, Sch. of Med. and Dentistry. Pp. 140; 4 ills. Springfield, Ill., Charles C Thomas, 1950. Price, $2.75.

THIS book examines the causes of an important symptom in medicine, for which there are many causes. Explanations of vasodepressor syncope are particularly well done. The role of fear is emphasized by the author whose appointments well qualify him to do so. The physiological bases used to elucidate the manifold causes are sound. The book is well arranged and useful. M. O.

The Handbook of Dream Analysis. By EMIL A. GUTHEIL, Dir. of Education, Inst. for Res. in Psychotherapy, Inc. 710 Pages; 85 ills. N. Y.: Liveright Publishing Corp., 1951. Price, $5.95.

THE Author, who is editor of the American Journal of Psychotherapy and a diplomate of the American Board of Neurology and Psychiatry, has spent 30 years in research and the practice of psychotherapy. He has produced an excellent book on the dream by: 1) drawing liberally from all who have contributed to dream analysis, 2) providing many helpful illustrations, 3) making a most practical application of dream analysis in a long chapter on dreams and the clinic, in which he has shown how dreams may help in understanding the psychopathology of cases seen daily in every physician's practice.

The Writer has that gift of synthesizing material from many fields in a way that makes reading on a difficult subject very interesting. The bibliography and index are extensive. O. E.

Das Werden der Homoopathie. By RUDOLF TISCHNER. Pp. 211. Stuttgart: Hippokrates-Verlag Marquardt & Cie. DM 13.50.

Serum Sickness. By C. FRH. VON PIRQUET, and BELA SCHICK, M.D., Transl. by BELA SCHICK, M.D. Pp. 130; 33 charts. Baltimore: Williams & Wilkins, 1951. Price, $3.50.

Newer Concepts of Inflammation. By VALY MENKIN, M.D., Assoc. Prof. of Exper. Pathol., Temple Univ. American Lect. Ser. 70. Pp. 152; 81 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $3.50.

Urgent Diagnosis without Laboratory Aid. By Prof. Dr. HANS L. BAUR, Univ. of Munich. American Lect. Ser. 66 Pp. 89. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.00.

Zur Frage der Cortison-Wirkung. Die "Corticogene Kettenreaktion". By Prof. BEIGLBOCK, Dr. H. HOFF, and R. CLOTTEN. Pp. 142. Augsburg: Hans Hoffe, 1951. Price, 6.50 DM.

Giardia intestinalis og Andre Tarmprotozoer hos Mennesket (with an English summary). By ERLING LUND. Pp. 199; 43 ills. Copenhagen: Ejnar Munksgaard, 1950. D.Cr.20/-.

Facts About the Menopause. By MAXINE DAVIS. Pp. 172. New York: McGraw-Hill. 1951. Price, $2.50.

Pain and its Problems. Edited by SIR HENEAGE OGILVIE and WILLIAM A. R. THOMSON, M.D. Pp. 194. London: Eyre & Spottiswoode, 1950. Price, 12s.6d. Philadelphia: Blakiston Co., 1950. Price, $3.00.

Diathermy. The Use of High Frequency Currents. By STAFFORD L. OSBORNE, M.S., Ph.D., Prof. and Chairm. Dept. Physical Med., Northwestern Univ. Amer. Lect. Series No. 91. Pp. 113; 63 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $3.00.

Introduction to Diophthalmology. By N. A. STUTTERHEIM, M.D., (Rand), State Med. Qualifications, Holland; formerly Surgeon to Eye Clinic, Univ. of Leiden. Pp. 43; 2 ills. London: H. K. Lewis, 1950. Price, 7s.6d.

The Antihistamines. Their Clinical Application. By SAMUEL M. FEINBERG, M.D., Assoc. Prof of Med., SAUL MALKIEL, Ph.D., M.D., Asst. Prof. of Med., and ALAN R. FEINBERG, M.D., Clinical Asst. in Med., Northwestern Univ. Med. Sch. Pp. 291. Chicago: Year Book Publishers, 1950. Price, $4.00.

Essays in the History of Medicine. By GEORGE GASK. Pp. 215. ills. London: Butterworth, 1950. Price, 1. 2/6.

NEW EDITIONS

The Eye Manifestations of Internal Diseases. By I. S. TASSMAN, M.D., Assoc. Prof. of Ophthalmol., Grad. Sch. of Med., Univ. of Pennsylvania; Attending Surgeon, Wills Eye Hospital, Phila. 3rd ed. Pp. 672; 279 ills. St. Louis: C. V. Mosby, 1951. Price, $12.00.

Anatomy of the Nervous System. By OLAF LARSELL, M.A., Ph.D., Sc.D., Prof. of Anatomy, Univ. of Oregon Med. Sch. 2nd ed. Pp. 520; 382 ills. New York: Appleton-Century-Crofts, Inc. Price, $9.00.

IN this 2nd edition Dr. Larsell presents a well-organized, readable description of the nervous system. The arrangement of the material, beginning with a review of the gross anatomy and the development of the brain and spinal cord, is but one of the many commendable features of the book. The Author's comprehensive knowledge of the subject and his experience as a teacher and investigator are reflected throughout the text.

Generalizations are used as a basis for explaining the structure and function of the intricate connections of the nervous system. This organization, the addition of a chapter on the circulation of the brain and spinal cord, and a selected bibliography at the end of each chapter make the book valuable, not only for the beginning student in neuroanatomy, but also for the practicing physician.

The illustrations are adequate and well positioned. Line diagrams and half tones throughout the text integrate gross relations and functional nervous pathways. It is regrettable that a few of the half tones are not better reproduced (for example, Figs. 11 and 59), and that Fig. 207 does not completely agree with the text description of the pathways illustrated. D. K.

The Normal Encephalogram. By LEO M. DAVIDOFF, M.D., Clin. Prof. of Neurosurg., New York Univ. Postgrad. Med. Sch., and CORNELIUS G. DYKE, M.D., late Prof. of Radiology, Coll. of Phys. and Surg., Columbia Univ. 3rd ed. Pp. 240; 190 ills. on 156 figs. Philadelphia: Lea & Febiger, 1951. Price, $6.00.

THE present edition of this authoritative volume is issued at this time, with relatively minor additions, as a companion volume to the new work by Drs. Davidoff and Epstein, "The Abnormal Encephalogram." "The Normal Encephalogram" is the standard textbook on the subject and is based on the authors' experience with thousands of encephalographic studies at the Neurological Institute, New York. H. S.

The Science of Health. By FLORENCE L. MEREDITH, M.D., Tufts College. 2nd ed. Pp. 452. Philadelphia: Blakiston Co., 1951. Price, $3.75.

THIS is a second edition, 9 years after the first, of a book for use in high school and college hygiene courses. The author is a member of the American Public Health and American Psychiatric Associations. The volume is replete with factual information about health and how to preserve it. There are numerous illustrations and a fairly large section is devoted to emotional hygiene. O. E.

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